1.3.1.1 Professional Information

SCHEDULING STATUS **S 4**

1 NAME OF THE MEDICINE

Europan 200 mg, 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pazopanib hydrochloride.

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

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

Pink film-coated capsule-shaped tablets, debossed with "173" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EUROPAN 200 mg 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 EUROPAN 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 EUROPAN 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 EUROPAN 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 pazopanib 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 in patients with hepatic impairment have not been fully established (see section 4.4).

Paediatric Population

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

Method of administration

For oral use.

EUROPAN 200 mg 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 pazopanib and other ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic Effects

Cases of hepatic failure (including fatalities) have been documented with the use of pazopanib. Pazopanib has not been studied in patients with pre-existing hepatic impairment and therefore should be used with caution in these patients. In studies with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin have been documented (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. Monitor serum liver tests before initiation of treatment with EUROPAN 200 mg and 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.

- Patients with isolated transaminase elevations ≤ 8 X ULN may continue on EUROPAN 200 mg with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
- Patients with transaminases of > 8 X ULN should have EUROPAN 200 mg interrupted until they return to Grade 1 or baseline. If the potential benefit for re-initiating EUROPAN 200 mg treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce EUROPAN 200 mg at a reduced dose and measure serum liver tests weekly for 8 weeks (see section 4.2). If transaminase elevations > 3 X ULN recur, then EUROPAN 200 mg should be discontinued.
- If transaminase elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, bilirubin fractionation should be performed. If direct (conjugated) bilirubin is > 35 % of total bilirubin, EUROPAN 200 mg should be discontinued.

Hypertension

Events of hypertension including newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crisis) have been documented with the use of pazopanib. Blood pressure should be

well controlled prior to initiating EUROPAN 200 mg. 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 ≥ 150 mm Hg or diastolic blood pressure ≥ 100 mm Hg) have been documented 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). Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of EUROPAN 200 mg (interruption and re-initiation at a reduced dose based on clinical judgement). EUROPAN 200 mg should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and EUROPAN 200 mg dose reduction (see sections 4.2 and 4.8).

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

PRES/RPLS have been documented 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 EUROPAN 200 mg in patients developing PRES/RPLS.

Interstitial lung disease (ILD)/ Pneumonitis

ILD, which can be fatal, have been documented in association with pazopanib (see section 4.8). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue pazopanib in patients developing ILD or pneumonitis.

Cardiac dysfunction/ Heart failure

The risks and benefits of EUROPAN 200 mg 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. Events of cardiac dysfunction such as congestive heart failure and decreased LVEF have been documented in association with pazopanib (see section 4.8). 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, 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 studies with pazopanib, events of QT prolongation or torsade de pointes have been documented (see section 4.8). EUROPAN 200 mg should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using EUROPAN 200 mg, periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

Arterial Thrombotic Events

In studies with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack have been documented (see section 4.8). EUROPAN 200 mg 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 studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have been documented.

Thrombotic microangiopathy (TMA)

In studies with pazopanib, TMA events have been documented (see section 4.8). Patients developing TMA should permanently discontinue treatment with pazopanib. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

Haemorrhagic Events

In studies with pazopanib haemorrhagic events have been documented (see section 4.8). EUROPAN 200 mg is not recommended in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. EUROPAN 200 mg 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 pazopanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal Perforations and Fistula

In studies with pazopanib, events of gastrointestinal (GI) perforation or fistula have been documented (see section 4.8). EUROPAN 200 mg 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 EUROPAN 200 mg should be stopped at least 7 days prior to scheduled surgery. The decision to resume EUROPAN 200 mg after surgery should be based on clinical judgement of adequate wound healing. EUROPAN 200 mg should be discontinued in patients with wound dehiscence.

Hypothyroidism

In studies with pazopanib, events of hypothyroidism have been documented (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 EUROPAN 200 mg treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction

on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria

In studies with pazopanib, proteinuria has been documented. Baseline and periodic urine analysis during treatment is recommended and patients should be monitored for worsening proteinuria. EUROPAN 200 mg 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 EUROPAN 200 mg. Patients at risk should be closely monitored and treated as clinically indicated.

Infections

Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been documented.

Pregnancy

If pazopanib is used during pregnancy, or if the patient becomes pregnant whilst receiving pazopanib, 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 (see section 4.6).

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 medicinal products 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 EUROPAN 200 mg (see section 4.5).

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

Concomitant administration of EUROPAN 200 mg 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 EUROPAN 200 mg (see section 4.5).

Paediatric population

The safety and efficacy of EUROPAN 200 mg in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on EUROPAN 200 mg

In vitro studies suggested that the oxidative metabolism of EUROPAN 200 mg 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 EUROPAN 200 mg.

CYP3A4, P-gp, BCRP inhibitors

EUROPAN 200 mg is a substrate for CYP3A4, P-gp and BCRP.

Studies documented concurrent administration of EUROPAN 200 mg (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 EUROPAN 200 mg $AUC_{(0-24)}$ and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). Pharmacokinetic parameter comparisons of EUROPAN 200 mg C_{max} (range of means 27.5 to 58.1 µg/ml) and $AUC_{(0-24)}$ (range of means 48.7 to 1040 µg*h/ml) after administration of EUROPAN 800 mg alone and after administration of EUROPAN 400 mg plus ketoconazole 400 mg (mean C_{max} 59.2 µg/ml, mean $AUC_{(0-24)}$1300

µg*h/ml) indicated that, in the presence of a strong CYP3A4 and P-gp inhibitor a dose reduction to EUROPAN 400 mg once daily will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg EUROPAN once daily alone. Some patients however may have systemic EUROPAN 200 mg exposure greater than what has been observed after administration of 800 mg EUROPAN alone.

Co-administration of EUROPAN 200 mg with other strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase EUROPAN 200 mg concentrations. Grapefruit juice contains an inhibitor of CYP3A4 and may also increase plasma concentrations of EUROPAN 200 mg.

Studies documented 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 EUROPAN resulted in an approximately 50 % to 60 % increase in mean EUROPAN 200 mg $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg EUROPAN alone. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to EUROPAN 200 mg.
Co-administration of EUROPAN 200 mg with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma EUROPAN 200 mg concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of EUROPAN 200 mg, including distribution into the central nervous systems (CNS).

Concomitant use of EUROPAN 200 mg with a strong CYP3A4 inhibitor should be avoided (see section 4.4). If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of EUROPAN 200 mg should be reduced to 400 mg daily during concomitant administration. 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 medicinal product with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4, P-gp, BCRP inducers

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

Effects of EUROPAN 200 mg on other medicinal products

In vitro studies with human liver microsomes documented that EUROPAN 200 mg 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. Pharmacology studies, using EUROPAN 800 mg once daily, have demonstrated that EUROPAN 200 mg 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. EUROPAN 200 mg resulted in an increase of approximately 30 % in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33 % to 64 % in the ratio of dextrometrophan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of EUROPAN 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* IC50 and *in vivo* plasma C_{max} values, EUROPAN 200 mg metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of EUROPAN 200 mg towards BCRP. Furthermore, inhibition of BCRP and P-gp by EUROPAN 200 mg in the gastrointestinal tract cannot be excluded. Care should be taken when EUROPAN 200 mg is co-administered with other oral BCRP and P-gp substrates.

In vitro, EUROPAN 200 mg inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that EUROPAN 200 mg will affect the pharmacokinetics of substrates of OATP1B1 (e.g. statins, see “Effect of concomitant use of EUROPAN 200 mg and simvastatin” below).

EUROPAN 200 mg 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 EUROPAN 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. EUROPAN 200 mg may have a greater impact on SN-38 disposition in patients with the UGT1A1*28 polymorphism relative to patients with the wild-type allele. However, the UGT1A1 genotype was not always predictive of the effect of EUROPAN 200 mg on SN-38 disposition. Care should be taken when EUROPAN 200 mg is co-administered with substrates of UGT1A1.

Effect of concomitant use of EUROPAN 200 mg and simvastatin

Concomitant use of EUROPAN 200 mg and simvastatin increases the incidence of ALT elevations. Studies documented that ALT > 3x ULN was reported 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 EUROPAN 200 mg 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 EUROPAN 200 mg will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).

Effect of Food on EUROPAN 200 mg

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

Medicinal products that raise gastric pH

Concomitant administration of EUROPAN 200 mg with esomeprazole decreases the bioavailability of EUROPAN 200 mg by approximately 40 % (AUC and C_{max}), and co-administration of EUROPAN 200 mg 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 EUROPAN 200 mg 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, EUROPAN 200 mg should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. EUROPAN 200 mg 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.

Paediatric population

The safety and efficacy of EUROPAN 200 mg in children have not been established.

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 EUROPAN 200 mg and to avoid becoming pregnant while receiving treatment with EUROPAN 200 mg.

Male patients (including those who have had vasectomies) should use condoms during sexual intercourse while taking EUROPAN 200 mg and for at least 2 weeks after the last dose of EUROPAN 200 mg to avoid potential exposure to the medicinal product for pregnant partners and female partners of reproductive potential.

Pregnancy

There are no adequate data from the use of EUROPAN 200 mg in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Breastfeeding

The safe use of EUROPAN 200 mg during breastfeeding has not been established. It is not known whether EUROPAN 200 mg or its metabolites are excreted in human milk. There are no animal data on the excretion of EUROPAN 200 mg in animal milk. A risk to the breastfed child cannot be excluded. Breastfeeding should be discontinued during treatment with EUROPAN 200 mg.

Fertility

Animal studies documented that male and female fertility may be affected by treatment with EUROPAN 200 mg.

4.7 Effects on ability to drive and use machines

EUROPAN 200 mg 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 EUROPAN 200 mg 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

Tabulated summary of adverse reactions

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

The following convention has been utilised for the classification of frequency:

Frequent, less frequent and frequency unknown

SOC category	Frequency	Side effect
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

SOC category	Frequency	Side effect
	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, Weight decreased, Anorexia
	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
	Less frequent	Hypoaesthesia, Transient ischaemic attack, Somnolence, Cerebrovascular accident, Ischaemic stroke, Posterior reversible encephalopathy/ reversible posterior leukoencephalopathy syndrome[†]

SOC category	Frequency	Side effect
Eye disorders	Frequent	Vision blurred
	Less frequent	Retinal detachment[†], Retinal tear[†], Eyelash discolouration
Cardiac disorders	Frequent	QT prolongation
	Less frequent	Bradycardia, Myocardial infarction, Cardiac dysfunction[f], Myocardial ischaemia, Torsade de Pointes
Vascular disorders	Frequent	Hypertension, Hot flush, Venous thromboembolic event[g], Flushing
	Less frequent	Hypertensive crisis, Haemorrhage, Cerebral haemorrhage
	Frequency unknown	Aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	Frequent	Epistaxis, Dysphonia, Dyspnoea, Haemoptysis
Respiratory, thoracic, and mediastinal disorders	Less frequent	Rhinorrhoea, Pulmonary haemorrhage, Pneumothorax, Interstitial lung disease/ pneumonitis[†]
Gastrointestinal disorders	Frequent	Diarrhoea, Nausea,

SOC category	Frequency	Side effect
		Vomiting, Abdominal pain[a], Stomatitis, Dyspepsia, Flatulence, Abdominal distention, 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
Hepatobiliary disorders	Frequent	Hyperbilirubinaemia, Hepatic function abnormal, Hepatotoxicity

SOC category	Frequency	Side effect
	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, Dry skin, Pruritus, Erythema, Skin depigmentation, Hyperhidrosis
	Less frequent	Nail disorders, Skin exfoliation, Photosensitivity reaction, Rash erythematous, Skin disorder, Rash macular, Rash pruritic, Rash vesicular, Pruritus generalised, Rash generalised, Rash papular, Plantar erythema
Musculoskeletal and	Frequent	Arthralgia,

SOC category	**Frequency**	**Side effect**
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	Less 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, Blood bilirubin increased, Blood creatinine increased, Lipase increased, White blood cell count decreased[d], Blood thyroid stimulating hormone increased, Amylase increase, Gamma-glutamyltransferase increased, Blood pressure increased Blood urea increased, Liver function test abnormal
	Less frequent	Hepatic enzyme increased,

SOC category	Frequency	Side effect
		Blood glucose decreased, Electrocardiogram QT prolonged, Transaminase increased, Thyroid function test abnormal, Blood pressure diastolic increased, Blood pressure systolic increased

† Spontaneous case reports documented from pazopanib use and adverse reactions documented from pazopanib studies.
* Spontaneous case reports documented from pazopanib use.

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

Paediatric population

The safety and efficacy of EUROPAN 200 mg in children have not been established.

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage

Pazopanib doses up to 2 000 mg have been evaluated in studies without dose limiting toxicity.

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

Category and class: 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 Cmax 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 - 100 µg/ml. *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

PovidoneK-30

Sodium starch glycolate

Magnesium stearate

Purified water

Opadry YS-1-14762-A Pink (Titanium dioxide, Hypromellose, Macrogol, Polysorbate 80, Iron oxide red)

6.2 Incompatibilities

Not known.

6.3 Shelf life

The shelf life is 36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

HDPE containers with child-resistant PP cap (with liner) and desiccant, 60 ml, 30 tablets/ container

HDPE containers with child-resistant PP cap (with liner) and desiccant, 100 ml, 90 tablets/ container

HDPE containers with child-resistant PP cap (with liner) and desiccant, 100 ml, 120 tablets/container

6.6 Special precaution for disposal

No special instructions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd

Woodmead Office Park,

3 Stirrup Lane

Van Reenens Avenue,

Woodmead, 2144

8 REGISTRATION NUMBER

To be allocated

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10 DATE OF REVISION OF THE TEXT