Applicant : Eurolab (Pty) Ltd
Proprietary name : Pazopanib Eurolab 200 mg & 400 mg
Dosage form and strength : Film-coated tablets; 200 mg & 400 mg
Date of submission : 21 April 2026
Approval date : 21 July 2026

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

PAZOPANIB 200 MG EUROLAB, 200 mg film-coated tablets

PAZOPANIB 400 MG EUROLAB, 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PAZOPANIB 200 MG EUROLAB:

Each film-coated tablet contains 200 mg pazopanib (as hydrochloride).

Sugar free.

PAZOPANIB 400 MG EUROLAB:

Each film-coated tablet contains 400 mg pazopanib (as hydrochloride).

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

PAZOPANIB 200 MG EUROLAB: Capsule-shaped, pink, film-coated tablet with “200” debossed on one side.

PAZOPANIB 400 MG EUROLAB: Capsule-shaped, white, film-coated tablet with “400” debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PAZOPANIB EUROLAB is indicated for the treatment of advanced and/or metastatic renal cell carcinoma

(RCC).

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

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

4.2 Posology and method of administration

Posology

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

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

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

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

Dose Modifications

Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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, therefore, use of PAZOPANIB EUROLAB is not recommended in these patients. 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). Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 ml/min.

Hepatic Impairment

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

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (see Pharmacological Properties- Pharmacokinetic properties: special populations).

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

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

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

Paediatric Population (below 18 years)

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

Method of administration

For oral use.

PAZOPANIB EUROLAB 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

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

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

Treatment with PAZOPANIB EUROLAB 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 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. 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 EUROLAB associated ALT elevations. Liver function should be monitored in all subjects receiving PAZOPANIB EUROLAB, 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 PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
- Patients with transaminases of > 8 X ULN should have PAZOPANIB EUROLAB interrupted until they return to Grade 1 or baseline. If the potential benefit for re-initiating PAZOPANIB EUROLAB treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce PAZOPANIB EUROLAB at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks (see section 4.2). If transaminase elevations > 3 X ULN recur, then PAZOPANIB EUROLAB 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, PAZOPANIB EUROLAB should be discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. PAZOPANIB EUROLAB is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of PAZOPANIB EUROLAB and simvastatin increases the risk of ALT elevations (see section 4.5) and should be undertaken with caution and close monitoring.

Beyond recommending that patients with mild hepatic impairment are treated with 800 mg PAZOPANIB EUROLAB 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

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 PAZOPANIB EUROLAB. 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 PAZOPANIB EUROLAB (interruption and re-initiation at a reduced dose based on clinical judgement). PAZOPANIB EUROLAB should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and

persists despite anti-hypertensive therapy and PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of PAZOPANIB EUROLAB (interruption and re-initiation at a reduced dose based on clinical judgment). 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). PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB, 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). PAZOPANIB EUROLAB should be used with caution in patients who are at increased risk for these events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months.
A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

Venous thromboembolic events

In studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have been documented. The incidence was higher in the STS population (5 %) than in the RCC population (2 %).

Thrombotic microangiopathy (TMA)

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

Haemorrhagic Events

In studies with pazopanib haemorrhagic events have been documented (see section 4.8). PAZOPANIB EUROLAB is not recommended in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. PAZOPANIB EUROLAB 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). PAZOPANIB EUROLAB 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 EUROLAB should be stopped at least 7 days prior to scheduled surgery. The decision to resume PAZOPANIB EUROLAB after surgery should be based on clinical judgement of adequate wound healing. PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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. PAZOPANIB EUROLAB 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 EUROLAB. Patients at risk should be closely monitored and treated as clinically indicated.

Pneumothorax

In studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have occurred (see section 4.8). Patients on pazopanib 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 documented.

Combination with other systemic anti-cancer therapies

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

agents.

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).

Juvenile animal toxicity

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

Paediatric population

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

Class effects

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in PAZOPANIB EUROLAB.

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

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

Interactions

Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to PAZOPANIB EUROLAB (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 pazopanib (see section4.5).

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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on PAZOPANIB EUROLAB

In vitro studies suggested that the oxidative metabolism of PAZOPANIB EUROLAB 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 EUROLAB.

CYP3A4, P-gp, BCRP inhibitors

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

Studies documented 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 µg/mL and $AUC_{(0-24)}$ (range of means 48,7 to 1040 µg*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 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 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 PAZOPANIB EUROLAB with other strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase PAZOPANIB EUROLAB concentrations. Grapefruit juice should be avoided as it contains an inhibitor of CYP3A4 and may also increase plasma concentrations of PAZOPANIB EUROLAB.

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

Concomitant use of PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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 medicine 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 PAZOPANIB EUROLAB concentrations. Co-administration of PAZOPANIB EUROLAB with potent P-gp or BCRP inducers may alter the exposure and distribution of PAZOPANIB EUROLAB, including distribution into the CNS. Selection of an alternative concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

Effects of PAZOPANIB EUROLAB on other medicines

In vitro studies with human liver microsomes documented 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. Pharmacology studies, using pazopanib mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30 % in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33 % to 64 % in the ratio of dextrometrophan to dextrophan 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 EUROLAB metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of PAZOPANIB EUROLAB towards BCRP. Furthermore, inhibition of BCRP and P-gp by PAZOPANIB EUROLAB in the gastrointestinal tract cannot be excluded. Care should be taken when PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB and simvastatin" below).

PAZOPANIB EUROLAB 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 EUROLAB 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 pazopanib on SN-38 disposition. Care should be taken when PAZOPANIB EUROLAB is co-administered with substrates of UGT1A1.

Effect of concomitant use of PAZOPANIB EUROLAB and simvastatin

Concomitant use of PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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 EUROLAB will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).

Effect of Food on PAZOPANIB EUROLAB

Administration of PAZOPANIB EUROLAB with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB with esomeprazole decreases the bioavailability of PAZOPANIB EUROLAB by approximately 40 % (AUC and C_{max}), and co-administration of PAZOPANIB EUROLAB 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 EUROLAB 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 EUROLAB 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 EUROLAB should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H_2-receptor antagonists are co-administered are based on physiological considerations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Female patients and female sexual partners of male patients receiving PAZOPANIB EUROLAB should be advised to avoid becoming pregnant and to use highly effective contraception until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 6 months after exposure (i.e. five half-lives after the last dose, plus 6 months which covers the growth and maturation phase of folliculogenesis).

Male patients treated with PAZOPANIB EUROLAB (including those who have had vasectomies) should be advised to use condoms, during sexual intercourse until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 3 months after exposure (i.e. five half-lives after the last dose, plus 60 to 75 days for sperm production

plus 10 to 14 days for the transport to the epididymis).

Pregnancy

PAZOPANIB EUROLAB should not be used during pregnancy.

There are no adequate data from the use of PAZOPANIB EUROLAB in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Women of childbearing potential should use adequate contraception and should not become pregnant while receiving treatment with PAZOPANIB EUROLAB.

Breastfeeding

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

Fertility

Animal studies documented that male and female fertility may be affected by treatment with PAZOPANIB EUROLAB.

4.7 Effects on ability to drive and use machines

PAZOPANIB EUROLAB 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 PAZOPANIB EUROLAB 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

Table 1 Adverse medicine reactions, by organ class and frequency

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)	Frequent	Tumour pain
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, Neutropenia, Leukopenia
	Less frequent	Polycythaemia, Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†
Endocrine disorders	Frequent	Hypothyroidism
Metabolism and nutrition disorders	Frequent	Decreased appetite[e], Hypophosphataemia, Dehydration, Weight decreased, Anorexia
	Less frequent	Hypomagnesaemia
	Frequency unknown	Tumour lysis syndrome*

SOC category	**Frequency**	**Side effect**
Psychiatric disorders	Frequent	Insomnia
Nervous system disorders	Frequent	Dysgeusia[c], Headache, Dizziness, Lethargy, Paraesthesia, Peripheral sensory neuropathy, Insomnia
	Less frequent	Hypoaesthesia, Transient ischaemic attack, 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, Bradycardia (asymptomatic), Myocardial ischaemia, Left ventricular dysfunction
	Less frequent	Myocardial infarction, Cardiac dysfunction[f], Torsade de Pointes
Vascular disorders	Frequent	Hypertension,

SOC category	Frequency	Side effect
		Hot flush, Venous thromboembolic event[g], Flushing, Gastrointestinal haemorrhage, Haematuria, Pulmonary haemorrhage
	Less frequent	Hypertensive crisis, Haemorrhage, Cerebral haemorrhage
	Frequency unknown	Aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	Frequent	Epistaxis, Dysphonia, Dyspnoea, Haemoptysis, Cough, Pneumothorax, Hiccups
	Less frequent	Rhinorrhoea, Interstitial lung disease/ pneumonitis[†], Oropharyngeal pain, Bronchial haemorrhage
Gastrointestinal disorders	Frequent	Diarrhoea, Nausea, Vomiting, Abdominal pain[a], Stomatitis,

SOC category	Frequency	Side effect
		Dyspepsia, Flatulence, Abdominal distention, Mouth ulceration, Dry mouth, Lipase elevations, Anal haemorrhage, Mouth haemorrhage
	Less frequent	Pancreatitis, Rectal haemorrhage, Haematochezia, Melaena, Frequent bowel movements, Large intestine perforation, Upper gastrointestinal haemorrhage, Enterocutaneous fistula, Haematemesis, Haemorrhoidal haemorrhage, Ileal perforation, Oesophageal haemorrhage, Retroperitoneal haemorrhage, Gastrointestinal perforation, Peritonitis
Hepatobiliary disorders	Frequent	Hyperbilirubinaemia, Hepatic function abnormal, Hepatotoxicity,
	Less frequent	Jaundice,

SOC category	Frequency	Side effect
		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, Exfoliative rash, Hair depigmentation, Nail disorders, Skin disorder
	Less frequent	Skin exfoliation, Photosensitivity reaction, Rash erythematous, Rash macular, Rash pruritic, Rash vesicular, Pruritus generalised, Rash generalised, Rash papular, Plantar erythema Skin ulcer

SOC category	**Frequency**	**Side effect**
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, Myalgia, Muscle spasms, 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, Chills, Vision blurred
	Less frequent	Mucous membrane disorder,
Investigations	Frequent	Weight deceased, 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,

SOC category	Frequency	Side effect
		Blood pressure increased, Blood urea increased, Liver function test abnormal, Ear, nose and throat examination abnormal[h] Blood cholesterol abnormal
	Less frequent	Hepatic enzyme increased, Blood glucose decreased, Electrocardiogram QT prolonged, Transaminase increased, Thyroid function test abnormal, Blood pressure diastolic increased, Blood pressure systolic increased, Platelet count decreased

† 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

h The majority of these cases describe mucositis

Neutropenia, thrombocytopenia and palmar-plantar erythrodysesthesia syndrome were observed more frequently in patients of East Asian descent.

The following drug reactions have been identified during post-approval use of PAZOPANIB EUROLAB.

Table 2 Adverse reactions identified during post-approval use.

SOC category	Frequency	Side effect
Infections and Infestations	Frequency unknown	Infections (with or without neutropenia -see Section 4.4).
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Frequency unknown	Tumour lysis syndrome (including fatal cases); see section Section 4.4.
Blood and lymphatic system disorders	Frequency unknown	Polycythaemia , Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome see section Section 4.4)
Nervous system disorders	Frequency unknown	Posterior reversible encephalopathy syndrome (see section Section 4.4) cerebrovascular accident, transient ischaemic attack, ischaemic stroke.
Eye disorders	Frequency unknown	Retinal detachment/tear
Respiratory, thoracic, and mediastinal disorders	Frequency unknown	Interstitial lung disease (ILD)/pneumonitis (see section Section 4.4)
Gastrointestinal disorders	Frequency unknown	Flatulence, Pancreatitis
Hepatobiliary disorders	Frequency unknown	Gamma-glutamyl transpeptidase

SOC category	Frequency	Side effect
		increased, Hepatic Failure (Including fatal events)
Musculoskeletal and connective tissue disorders	Frequency unknown	Arthralgia, Muscle spasms

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za.

4.9 Overdose

Overdosage

Pazopanib doses up to 2 000 mg have been evaluated in studies without dose limiting toxicity. Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2 000 mg and 1 000 mg daily, respectively.

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. Treatment should be supportive and symptomatic. Cardiovascular monitoring for dysrhythmias and hypertension is required. Hepatic function should be assessed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 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).

Administration of a single PAZOPANIB 400 mg EUROLAB crushed tablet increased $AUC_{(0-72)}$ by 46 % and C_{max} by approximately 2- fold and decreased t_{max} by approximately 1,5 hours compared to

administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to whole tablet. Therefore due to this potential for increased exposure, tablets should not be crushed (see Section 4.2).

Distribution

Binding of pazopanib to human plasma protein *in vivo* 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.

Special populations

Renal impairment

In a population pharmacokinetic analysis, creatinine clearance (30-150 ml/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance $\geqslant$ 30 ml/min (see Section 4.2)

Hepatic Impairment

The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up

to 1.5 X ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 µg/ml, range 12.5 47.3 and 841.8 µg.hr/ml, range 600.4 1078) are similar to the median in patients with no hepatic impairment (49.4 µg/ml, range 17.1-85.7 and 888.2 µg.hr/ml, range 345.5-1482) (see section 4.2).

The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1,5 X to 3 X ULN regardless of the ALT values) was 200 mg once daily. The median steady-state values of C_{max} (22.4 µg/ml, range 6.4-32.9) and $AUC_{(0-24)}$ (350,0 µg.hr/ml, range 131,8-487,7) after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45 % and 39 %, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function (see section 4.2).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Povidone K-30

Sodium starch glycolate

Magnesium stearate

Purified water

Coating material (Titanium dioxide E171, Hypromellose E464, Macrogol 400 E1521, Polysorbate 80 E433, Iron oxide red E172)

6.2 Incompatibilities

Not known.

6.3 Shelf life

The shelf life is 48 months.

6.4 Special precautions for storage

Store at or below 25 °C. Keep in the outer carton until required for use.

6.5 Nature and contents of container

PAZOPANIB 200 MG EUROLAB:

White HDPE bottles with a polypropylene child-resistant cap of 30 or 90 tablets.

Clear/transparent Aluminium-PVC/PE/PVDC blisters of 30, 60 or 90 tablets.

PAZOPANIB 400 MG EUROLAB:

White HDPE bottles with a polypropylene child-resistant cap of 30 or 60 tablets.

Clear/transparent Aluminium-PVC/PE/PVDC blisters of 30, 60 or 90 tablets.

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

PAZOPANIB 200 MG EUROLAB: 56/26/0345

PAZOPANIB 400 MG EUROLAB: 56/26/0346

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 July 2025

10 DATE OF REVISION OF THE TEXT

21 July 2026