PACHTOR® PAZOPANIB 200 mg – 400 mg

Coated tablets

Argentine Industry Prescription drug only

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each coated Tablet of PACHTOR contains:

Pazopanib (as Pazopanib Hydrochlorhydrate) 200 mg 66.129 mg Sodium starch glycollate 19.2 mg Povidone 16 mg 2.5 mg 3.2 mg Colloidal silicon dioxide Magnesium stearate 2.125 mg Hydroxypropylmethylcellulose Talc powder 1 mg Polyethylene glycol 2 mg Titanium dioxide (CI: 77891) Ferric oxide red (CI: 77491) 1.125 mg

Each coated tablet of 400 mg contains:

| Pazopanib (as Pazopanib Hydrochloride) | 400 mg |
|--|-----------|
| Lactose | 132.36 mg |
| Sodium starch glycollate | 38,4 mg |
| Povidone | 32.0 mg |
| Colloidal silicon dioxide | 5 mg |
| Magnesium stearate | 6.4 mg |
| Hydroxypropylmethylcellulose | 4.25 mg |
| Talc powder | 2 mg |
| Polyethylene glycol | 4 mg |
| Titanium dioxide (CI: 77891) | 2.25 mg |

Titanium dioxide (CI: 77891) Indications

Renal Cell Carcinoma (RCC)

PACHTOR® It is indicated for the first-line treatment of advanced Renal Cell Carcinoma (RCC) in adults and for patients with advanced disease who have received prior treatment with cytokines.

<u>Soft Tissue Sarcoma (STB)</u> PACHTOR® 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 and/or adjuvant therapy. Efficacy and safety have only been established in certain STS histological tumor subtypes

Pharmacodynamic properties

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

ATC code: L01XE11 Mechanism of action

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 ICSO values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFz, c-Kit and PDGFR- β receptors in cells. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, $angiogenes is in various \ animal \ models, and the growth \ of \ multiple \ human \ tumor \ xeno grafts \ in \ mice.$

Pharmacokinetic properties

Absorption

Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumors, maximum plasma concentration (C_{max}) of approximately 19 \pm 13 μ g/ml was obtained after median 3.5 hours (range 1.0-11.9 hours) and an AUCo $_{\odot}$ of approximately 650 \pm 500 μ g.h/ml was obtained. Daily dosing results in 1.23- to 4-fold increase in AUCo $_{\odot}$. There was no consistent increase in AUC or C $_{\odot}$ at pazopanib doses above 800 mg. Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least two hours after food or at least one hour before food. Administration of a pazopanib 400 mg crushed tablet increased AUC $_{\tiny{(0.72)}}$ by 46% and $C_{\tiny{max}}$ by approximately 2-fold and decreased $T_{\tiny{max}}$ by approximately 2 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 administration of the whole tablet.

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

<u>Biotransformation</u> Results from in vitro studies demonstrated that metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6% of

the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure. **Elimination**

Pazopanib is eliminated slowly with a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered

dose.

Special populations Renal impairment: Results indicate that less than 4% of an orally administered pazopanib dose is excreted in the

urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 ml/min to 150 ml/min) 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 Hepatic Impairment. Mild:

The median steady-state pazopanib C_{max} and $AUC_{(0-24\,h)}$ 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. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities of serum liver tests. Moderate:

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.

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

Severe:

with moderate hepatic impairment.

800 mg per day

The median steady-state C_{max} and AUC $_{(0.20)}$ 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). Table: Median steady state pazopanib pharmacokinetics measured in subjects with hepatic impairment Group Normal liver Research dose Cmax (ug/ml) AUC (0-24) (ug x hr./ml) Recommended dose

function (17.1-85.7) (345.5-1482) 800 mg per day 800 mg per day Mild liver

888.2

800 mg per day

52.0

| aystutiction | | (11.3-104.2) | (214.7-2034.4) | | | |
|---|----------------|--------------|----------------|-----------------|--|--|
| Moderate liver | 200 mg per day | 22.2 | 256.8 | 200 mg per day | | |
| dysfunction | | (4.2-32.9) | (65.7-487.7) | | | |
| Severe liver | 200 mg per day | 9.4 | 130.6 | Not recommended | | |
| dysfunction | , i | (2.4-24.3) | (46.9-473.2) | | | |
| Dosage and Administration PACHTOR® treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products. | | | | | | |

Dosage

Adults The recommended dose of pazopanib for the treatment of RCC or STS is 800 mg once daily Dose modifications Dose modification (decrease or increase) should be in 200 mg decrements or increments in a stepwise fashion

Pediatric population

Pazopanib should not be used in children younger than 2 years of age because of safety concerns with regard to organ growth and maturation. The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established. No data

based on individual tolerability to manage adverse reactions. The dose of pazopanib should not exceed 800 mg.

are available.

Elderly
There are limited data on the use of pazopanib in patients aged 65 years and older. In the RCC studies of pazopanib, overall, no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in responses

between the elderly and younger patients, but greater sensitivity of some elderly patients cannot be ruled out.

Renal Impairment

Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites. Therefore, 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.

in patients with varying degrees of hepatic dysfunction. All patients should have liver function tests to

Hepatic impairment Dosing recommendations in hepatically impaired patients are based on pharmacokinetic studies of pazopanib

determine whether they have hepatic impairment before starting and during pazopanib therapy. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring of tolerability. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities in serum liver tests (defined either as normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or as an elevation of bilirubin (>35% direct) up to 1.5 x upper limit of normal (ULN) regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (defined as an elevation of bilirubin >1.5 to $3 \times$ ULN regardless of the ALT value)

<u>Administration</u>
Pazopanib should be taken without food, at least one hour before or two hours after a meal. PACHTOR* film-coated tablets should be taken whole with water and not broken or crushed.

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin

Contraindications $\label{prop:substance} \mbox{Hypersensitivity to the active substance or to any of the excipients.}$

>3 x ULN regardless of the ALT value).

Special warnings and precautions for use Hepatic toxicity and Liver dysfunction

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

abnormalities in serum liver tests (either normal bilirubin and any degree of ALT elevation or elevation of bilirubin up to 1.5 x ULN regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (elevation of bilirubin > 1.5 to 3 x ULN regardless of the ALT value). Pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin > 3

x ULN regardless of the ALT value). 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. In most 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.

Serum liver tests should be performed before initiation of treatment with pazopanib, at weeks 3, 5, 7 and 9, then at months 3 and 4, with additional tests as clinically indicated. Periodic testing should then continue after month - Patients with isolated transaminase elevations ≤ 8 x upper limit of normal (ULN) can continue pazopanib with

weekly monitoring of liver function until transaminases return to Grade 1 or baseline. - Patients with transaminase elevation of >8 x ULN should interrupt pazopanib until transaminases return to Grade 1 or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the

risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and perform serum liver

- $tests\ weekly\ for\ 8\ weeks. Following\ reintroduction\ of\ pazopanib, if\ transaminase\ elevations\ > 3\ x\ ULN\ recur,\ then$ pazopanib should be discontinued. If transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN occur, permanently discontinue pazopanib. Patients should be monitored until return to Grade 1 or baseline. Pazopanib 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 and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring (see Interaction with other medicinal products and other forms of interaction). There are insufficient data available to analyze the risk of concomitant administration of pazopanib and other

statins. Patients older than 60 years may have a higher risk of an increase in ALT, from moderate (> 3 x ULN) to severe (>

8 x ULN).

Hypertension

In clinical studies with pazopanib, events of hypertension including newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crisis) have occurred. Blood pressure should be well controlled prior to initiating pazopanib. 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) occurred early in the course of treatment (approximately 40% of cases occurred by day 9 and approximately 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of pazopanib (interruption and re-initiation at a reduced dose based on clinical judgement). Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction.

<u>Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leukoencephalopathy syndrome (RPLS).</u>
PRES/RPLS has been reported in association with pazopanib. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness, and other visual and neurological disturbances, and can be fatal. Patients developing PRES/RPLS should permanently discontinue treatment with pazopanib.

Cardiac dysfunction/Heart failure

The risks and benefits of pazopanib 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, cardiac dysfunction events such as congestive heart failure and decreased

0.05 mg

Previous treatment with anthracyclines may be a risk factor for cardiac dysfunction.

Management: Treatment of hypertension (refer to hypertension warning section above) should be combined

with pazopanib dose interruptions and / or reductions in patients with significant LVEF decreases, as indicated clinical practice. 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, including previous exposure to anthracyclines.

QT interval prolongation and Torsade de Pointes. In clinical studies with pazopanib, events of QT prolongation and torsade de pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medicinal products that may prolong QT interval and in patients with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of

patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based on the assessment of individual patient's benefit/risk.

In clinical studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. While observed in both RCC and STS studies, the incidence was higher in the STS population (5%) than in the RCC population (2%).

Thrombotic microangiopathy Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), have been reported in clinical trials of pazopanib alone, in combination with bevacizumab, and in combination with topotecan.

<u>Hemorrhage events</u>
In clinical studies with pazopanib hemorrhagic events have been reported. Fatal hemorrhage events have occurred. Pazopanib has not been studied in patients who had a history of hemoptysis, cerebral hemorrhage or clinically significant gastrointestinal (GI) hemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of hemorrhage.

occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

growth factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound

standard medical practice before initiating pazopanib treatment. All patients should be closely monitored for signs and symptoms of thyroid dysfunction during treatment with pazopanib. Thyroid function should be monitored regularly and treated as standard medical practice. <u>Proteinuria</u>

reduction. Interstitial lung disease (ILD) / Pneumonitis ILD / pneumonitis, which can be fatal, has been reported in association with pazopanib. In clinical trials, ILD / pneumonitis occurred in 0.1% of pazopanib-treated patients.

Patients should be monitored for pulmonary symptoms suggestive of ILD / pneumonitis and pazopanib

treatment should be discontinued in patients who develop ILD or pneumonitis.

Pneumothorax

Increased toxicity in developmental organs

Administration of pazopanib to young rats less than 21 days of age resulted in toxicity to the lungs, liver, heart, and kidneys and death at doses significantly lower than the clinically recommended dose or tolerated dose in older animals. age. Pazopanib can potentially cause serious adverse effects on organ development in pediatric patients, especially in patients younger than 2 years of age, therefore PACHTOR should not be administered to

pediatric patients younger than 2 years of age. Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported. Patients should be monitored for signs and symptoms of infection, appropriate treatment instituted promptly,

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 stopped earlier than planned due to increased toxicity and / or mortality, and a

safe and effective dose combination for these treatments. PACHTOR is not indicated for use with other cancer Pregnancy

the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with pazopanib. **Interactions** Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp), or breast cancer resistant protein (BCRP) should be avoided due to the risk of increased exposure to pazopanib. An alternative selection of concomitant drugs with no or minimal potential to inhibit CYP34A, P-gp or BCRP should be considered.

Grapefruit juice should be avoided during treatment with pazopanib. Interaction with other medicinal products and other forms of interaction

CYP3A4 may alter the metabolism of pazopanib.

Effects of other medicinal products on pazopanib

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

Concomitant administration of pazopanib (400 mg once daily) with a strong CYP3A4 and P-gp inhibitor,

ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a mean increase in AUC $_{0.240}$ and of pazopanib C_{max} by 66% and 45% respectively, compared to pazopanib alone (400 mg once daily for 7 days). Comparison of pharmacokinetic parameters of C, (mean range 27.5 to 58.1 ug / ml) and AUC (2.3) (mean range

indicates that in the presence of a potent inhibitor of CYP3A4 and P-gp, dose reduction to 400 mg pazopanib once daily will produce a systemic exposure similar to that seen after 800 mg pazopanib once daily in most patients. However, some patients may have a systemic exposure to pazopanib greater than that observed after administration of 800 mg of pazopanib alone. Concomitant administration of pazopanib with other strong CYP3A4 family inhibitors (e.g, itraconazole clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice contains a CYP3A4 inhibitor and may also increase plasma concentrations of pazopanib.

Administration of 1,500 mg of lapatinib (weak CYP3A4 and P-gp substrate and inhibitor and strong BCRP inhibitor) with 800 mg of pazopanib produced an approximately 50% to 60% increase in mean AUC $_{\tiny{10.24}}$ and the $C_{\tiny{max}}$ of pazopanib, compared to the administration of 800 mg of pazopanib alone. Inhibition of P-gp and / or BCRP by lapatinib is likely to contribute to increased exposure of pazopanib. Concomitant administration of pazopanib with CYP3A4, P-gp and BCRP inhibitors, such as lapatinib, will result in increased plasma concentrations of pazopanib. Concomitant administration with strong P-pg or BCRF

Concomitant administration of pazopanib with a strong CYP3A4 inhibitor should be avoided. If a medically acceptable alternative to a strong CYP3A4 inhibitor is not available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration. In these cases, particular attention should be paid to $drug\text{-}related\ adverse\ reactions, and\ further\ dose\ reductions\ may\ be\ considered\ if\ potential\ drug\text{-}related\ adverse\ adverse\ drug\text{-}related\ adverse\ drug\text{$ reactions are observed.

Therefore, combination with strong P-gp or BCRP inhibitors should be avoided, or it is recommended to select an alternative concomitant medication that has no or minimal ability to inhibit P-gp or BCRP.

CYP3A4, P-gp, BCRP inducers CYP3A4 inducers such as rifampin may decrease plasma concentrations of pazopanib. Concomitant administration of pazopanib with a strong inducer of P-gp or BCRP may alter the exposure and distribution of pazopanib, including the distribution in the CNS. It is recommended to select an alternative concomitant medication that does not have the capacity or that has a minimal capacity for enzyme induction or transport.

In clinical pharmacology studies in cancer patients using 800 mg pazopanib once daily, pazopanib has been

shown to have no clinically relevant effect on the pharmacokinetics of caffeine (CVP1A2 substrate probe), warfarin (CYP2C9 substrate probe), or omeprazole (CYP2C19 substrate probe). Pazopanib causes an approximately 30% increase in the mean AUC and C_{\max} of Midazolam (CYP3A4 substrate probe) and increases of 33% to 64% in the ratio of dextromethorphan to dextrophan concentrations in urine after administration. oral dextromethorphan (CYP2D6 substrate probe). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg / m2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 25% and 31% respectively in paclitaxel AUC and max

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

Pazopanib is an in vitro inhibitor of the enzyme Uridine diphosphoglucuronosyl-transferase 1A1 (UGT1A1). The active metabolite of irinotecan, SN-38, is a substrate for OATP1B1 and UGT1A1. Co-administration of pazopanib 400 mg once daily with cetuximab 250 mg / m2 and irinotecan 150 mg / m2 resulted in an increase in systemic exposure to SN-38 of approximately 20%. Pazopanib may have a greater impact on SN-38 disposition in subjects with familial polymorphism in UGT1A1 * 28 than in subjects with the normal allele. However, the UGT1A1

genotype was not always predictive of the effect of pazopanib on SN-38 disposition. Caution should be exercised when pazopanib is co-administered with UGT1A1 substrates. Effect of concomitant use of pazopanib and simvastatin Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. If a patient receiving simvastatin simultaneously develops elevations in ALT, follow the dosing instructions for pazopanib and

pravastatin, rosuvastatin) Effect of food on pazopanib

should be avoided.

Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and C_{max}), and the co-administration of pazopanib with drugs that increase gastric pH

Consider using short-acting antacids instead of proton pump inhibitors (PPIs) and H2 receptor antagonists. Pazopanib should be administered at least 1 hour before or 2 hours after the administration of fast-acting

antacids.

LVEF have occurred Risk factors: Hypertension could exacerbate cardiac dysfunction in patients at risk through increased cardiac afterload

 $electrolytes \, (e.g. \, calcium, \, magnesium, \, potassium) \, within \, normal \, range \, is \, recommended.$ Arterial thrombotic events In clinical studies with pazopanib, myocardial infarction, myocardial ischemia, ischemic stroke, and transient ischemic attack were observed. Fatal events have been observed. Pazopanib should be used with caution in

Venous thromboembolic events

Patients who develop TMA should permanently discontinue treatment with pazopanib. After stopping treatment, it has been observed that the effects of MAT reverse. Pazopanib is not indicated for use in combination with other medicinal products.

<u>Gastrointestinal (GI) perforations and fistula</u> In clinical studies with pazopanib, events of GI perforation or fistula have occurred. Fatal perforation events have

Wound Healina No formal studies of the effect of pazopanib on wound healing have been conducted. Since vascular endothelial

Hypothyroidism Hypothyroidism has occurred in clinical trials with pazopanib. Reference values for thyroid function are recommended to be tested in the laboratory and patients with hypothyroidism should be treated according to

Cases of proteinuria have been reported in clinical trials with pazopanib. Baseline and periodic urinalysis during treatment is recommended- with 24-hour proteinuria monitoring according to clinical indication - as well as monitoring patients in case of worsening proteinuria. Pazopanib treatment should be discontinued and the dose reduced in case of 24-hour proteinuria ≥ 3 grams; discontinue pazopanib if episodes recur despite dose

In clinical studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have Occurred. Patients on pazopanib treatment should be observed closely for signs and symptoms of pneumothorax

The safety and efficacy of pazopanib in pediatric patients has not been established. Pazopanib is not indicated for use in pediatric patients. Based on its mechanism of action, pazopanib can have serious effects on organ growth and maturation during early postnatal development.

and consideration of discontinuation or discontinuation of pazopanib in the case of serious infections

re-clinical studies in animals have shown reproductive toxicity. If pazopanib is used during pregnancy, or if the patient becomes pregnant whilst receiving pazopanib, the potential hazard to the fetus should be explained to

Concomitant treatment with CYP34A inducers should be avoided due to the risk of decreased exposure to pazopanib. Cases of hyperglycemia have been observed during concomitant treatment with ketoconazole.

Caution should be exercised with concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) as pazopanib is an inhibitor of UGT1A1.

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of

Comparison of pharmaconimeter, parameters of ζ_{max} (mean range 27.5 to 35.1 μ g/ ml) and AUC $\zeta_{0.26}$ (mean range 48.7 to 1040 μ g * h / ml) after administration of 800 mg of pazopanib alone and after administration of 400 mg of pazopanib together with 400 mg of ketoconazole (mean C_{max} 59.2 μ g / ml, mean AUC $\zeta_{0.26}$ 1300 μ g * h / ml)

inhibitors may also alter the exposure and distribution of pazopanib, including distribution in the central nervous system (CNS).

Effects of pazopanib on other drugs In vitro studies with human liver microsomes showed that pazopanib inhibits CYP 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1 enzymes. The ability to induce CYP3A4 in humans was demonstrated in an in vitro assay of human PXR.

Based on in vitro ICSO values and in vivo plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib on BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Caution should be exercised when pazopanib is co-administered with other oral BCRP and P-gp substrates.

discontinue treatment with simvastatin. Furthermore, the concomitant use of pazopanib and other statins should be done with caution as currently insufficient data are available to assess their impact on ALT levels. It cannot be ruled out that pazopanib affects the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin,

Administration of pazopanib with high- or low-fat meals results in an approximately 2-fold increase in AUC and Cmax. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after meals. Medications that increase gastric pH

If the doctor considers it necessary to use a proton pump inhibitor (PPI) concomitantly, it is recommended to take the pazopanib dose in the absence of food, once a day in the evening together with the PPI. If the doctor

considers it necessary to use an H2 receptor antagonist concomitantly, pazopanib should be taken in the absence of food at least 2 hours before or 10 hours after taking an H2 receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after the administration of short-acting antacids. Recommendations on how to administer pazopanib together with PPIs and H2 receptor antagonists are based on physiological considerations.

Fertility, pregnancy and breast-feeding

<u>Pregnancy</u>
There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown

Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with pazopanib. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the fetus should be explained to the patient.

Women of childbearing potential should be advised to use adequate contraception to avoid becoming pregnant during treatment with pazopanib.

Breast-feeding
The safe use of pazopanib during breast-feeding has not been established. It is not known whether pazopanib

There are no animal data on the excretion of pazopanib in animal milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment

Animal studies indicate that male and female fertility may be affected by treatment with pazopanib.

with pazopanib. **Fertility**

Effects on ability to drive and use machines No studies on the effects on the ability to drive and use machines have been performed. 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 should be borne in mind when considering the patient's ability to rform tasks that require judgement, motor, or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired, or weak.

Adverse reactions

The most important serious adverse reactions identified in the RCC or STS studies were transient ischemic attack, ischemic stroke, myocardial ischemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation, and pulmonary, gastrointestinal and cerebral hemorrhage, all adverse reactions being reported in < 1 % of treated patients. Other important serious adverse reactions identified in STS studies included venous thromboembolic events, left ventricular dysfunction and pneumothorax. Other potentially serious adverse reactions are hepatotoxicity, thrombotic microangiopathy, posterior

reversible leukoencephalopathy syndrome, hypertension, infection, and increased toxicity with other antineoplastic therapies. Fatal events possibly associated with pazopanib included gastrointestinal bleeding, pulmonary bleeding /

hemoptysis, abnormal liver function, intestinal perforation, and ischemic stroke.

The most common adverse reactions (experienced by at least 10% of the patients) of any grade in the RCC and

STS trials included: diarrhea, hair color change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Adverse drug reactions, all grades, which were reported in RCC and STS subjects or during the post-marketing period are listed below by MedDRA body system organ class, frequency, and grade of severity. The following convention has been utilized for the classification of frequency:

- Common ≥1/100 a <1/10
- Uncommon ≥1/1.000 a <1/100 Rare ≥1/10.000 a <1/1.000 Very rare < 1/10 000
- Not known (cannot be estimated from the available data)

| lable 1. Heatment related | l adverse reactio | ons reported in RCC studies (n = | 1149) or dur | ng post-ma | rketing peri |
|---|-------------------------------------|---|----------------------------------|---------------------------------|------------------------------|
| System Organ Class Frequency Infections and | Frequency (all grades) | Adverse reactions Infections (with or without neutropenia) † | All grades n (%) not known | Grade 3 n (%) | Grade 4 n (%) not know |
| Infestations Neoplasms benign, | Uncommon Uncommon Common | Gingival infection Infectious peritonitis Tumor pain | 1 (<1%) 1 (<1%) 1 (<1%) | 0 0 1 (<1%) | 0 0 0 |
| malignant and inspecified (incl cysts and polyps) | | | | | |
| Blood and lymphatic system disorders | Common Common | Thrombocytopenia Neutropenia | 80 (7%) 79 (7%) | 10 (<1%) | 5 (<1%) 4 (<1%) |
| Endocrine disorders Metabolism and nutrition | Common Common Very common | Leucopenia Hypothyroidism Decreased apetite ^e | 63 (5%) 83 (7%) 317 (28%) | 5 (<1%) 1 (<1%) 14 (1%) | 0 0 |
| disorders | Common Common | Hypophosphatemia Dehydration | 21 (2%) | 7 (<1%) | 0 |
| Psychiatric disorders | Uncommon Common | Hypomagnesemia Insomnia | 10 (<1%) 30 (3%) | 0 | 0 |
| Nervous system disorders | Very common Very common | Dysgeusia c Headache | 254 (22%) 122 (11%) | 1 (<1%) | 0 |
| | Common Common | Dizziness Lethargy Paresthesia | 55 (5%) 30 (3%) 20 (2%) | 3 (<1%) 3 (<1%) 2 (<1%) | 1 (<1%) 0 0 |
| | Common Uncommon | Peripheral sensory neuropathy Hypoesthesia | 17 (1%) | 0 | 0 |
| | Uncommon Uncommon | Transient ischemic attack Somnolence | 7 (<1%) | 4 (<1%) 1 (<1%) | 0 |
| | Uncommon Uncommon | Cerebrovascular accident Ischemic stroke | 2 (<1%) 2 (<1%) | 1 (<1%) 0 | 1 (<1%) 1 (<1%) |
| Eyes disorders | Uncommon | Vision Blurred Eyelash discoloration | 19 (<2%) | 1 (<1%) | 0 |
| Cardiac disorders | Uncommon Uncommon | Bradycardia Myocardial infarction | 6 (<1%) 5 (<1%) | 1 (<1%) | 0 4 (<1%) |
| Vascular disorders | Uncommon Uncommon Very common | Cardiac dysfunction ^f Myocardial ischemia Hypertension | 4 (<1%) 3 (<1%) 473 (41%) | 1 (<1%) 1 (<1%) 115 (10%) | 0 0 1 (<1%) |
| | Common Common | Hot flush Venous thromboembolic | 16 (1%) 13 (1%) | 0 6 (<1%) | 0 7 (<1%) |
| | Common | event ⁹ Flushing | 12 (1%) | 0 | 0 |
| | Uncommon Uncommon | Hypertensive crisis Hemorrhage | 6 (<1%) 1 (<1%) | 0 | 2 (<1%) |
| Respiratory, thoracic and mediastinal disorders | Common Common | Epistaxis Dysphonia | 50 (4%) 48 (4%) | 1 (<1%) | 0 |
| | Common Common | Dyspnoea Hemoptysis | 42 (4%) 15 (1%) | 8 (<1%) | 1 (<1%) |
| | Uncommon Uncommon | Rhinorrhea Pulmonary Hemorrhage Pneumothorax | 8 (<1%) 2 (<1%) 1< (1%) | 0 0 | 0 0 |
| Gastrointestinal disorders | Very common Very common | Diarrhea Nausea | 614 (53%_) | 65 (6%) 14 (1%) | 2 (<1%) |
| uisorders | Very common Very common | Vomiting Abdominal pain a | 225 (20%) 139 (12%) | 18 (2%) 15 (1%) | 1 (<1%) |
| | Common Common | Stomatitis Dyspepsia | 96 (8%) 83 (7%) | 4 (<1%) | 0 |
| | Common Common | Flatulence Abdominal distension | 43 (4%) 36 (3%) | 0 2 (<1%) | 0 |
| | Common Common | Mouth ulceration Dry mouth | 28 (2%) 27 (2%) | 3 (<1%) | 0 |
| | Uncommon Uncommon | Pancreatitis Rectal hemorrhage | 8 (<1%) 8 (<1%) | 4 (<1%) 2 (<1%) | 0 |
| | Uncommon Uncommon | Hematochezia Gastrointestinal hemorrhage | 6 (<1%) | 2 (<1%) | 0 |
| | Uncommon Uncommon | Melena Frequent bowel movements | 4 (<1%) 3 (<1%) | 1 (<1%) | 0 |
| | Uncommon Uncommo | Anal hemorrhage Large intestine | 2 (<1%) | 0 1 (<1%) | 0 |
| | Uncommon | perforation Mouth hemorrhage | 2 (<1%) | 0 | 0 |
| | Uncommon | Upper gastrointestinal hemorrhage | 2 (<1%) | 1 (<1%) | 0 |
| | Uncommon Uncommon | Enterocutaneous fistula Hematemesis | 1 (<1%) | 0 | 0 |
| | Uncommon Uncommon | Hemorrhoidal hemorrhage Ileal perforation Esophagial hemorrhage | 1 (<1%) 1 (<1%) 1 (<1%) | 0 0 0 | 0 1 (<1%) 0 |
| Hepatobiliary disorders | Uncommon Common | Retroperitoneal hemorrhage Hyperbilirubinaemia | 1 (<1%) | 0 2 (<1%) | 0 1 (<1%) |
| reputos.mary alsoracis | Common Common | Abnormal liver function Hepatotoxicity | 29 (3%) 18 (2%) | 13 (1%) | 2 (<1%) |
| | Uncommon Uncommon | Jaundice Drug induced liver injury | 3 (<1%) 2 (<1%) | 1 (<1%) 2 (<1%) | 0 |
| Skin and subcutaneous | Uncommon Very common | Liver failure Hair color change | 1 (<1%) 404 (35%) | 0 1 (<1%) | 1 (<1%) 0 |
| disorders | Very common | Palmar-plantar erythrodysesthesia | 206 (18%) | 39 (3%) | 0 |
| | Very common | syndrome Alopecia Rash | 130 (11%) | 7 (<1%) | 0 |
| | , common | Skin hypopigmentation | 52 (5%) | 0 | 0 |
| | | Dry skin Pruritus | 50 (4%) 29 (3%) | 0 | 0 |
| | Common | Erythema Skin depigmentation | 25 (2%) 20 (2%) | 0 | 0 |
| | | Hyperhidrosis Nail disorders | 17 (1%) | 0 | 0 |
| | | Skin exfoliation Photosensitivity reaction | 7 (<1%) | 0 | 0 |
| | | Rash erythematous Skin disorder | 6 (<1%) | 0 | 0 |
| | Uncommon | Rash macular Rash pruritic | 4 (<1%) 3 (<1%) | 0 | 0 |
| | | Rash vesicular Generalized pruritus | 3 (<1%) 2 (<1%) | 0 1 (<1%) | 0 |
| | | Generalized rash Papuar rash | 2 (<1%) 2 (<1%) | 0 | 0 |
| Musculoskeletal and | Common | Plantar erythema Arthralgia | 1 (<1%) 48 (4%) | 0 8 (<1%) | 0 |
| connective tissue disorders | Common Common Uncommon | Myalgia Muscle spams Musculoskeletal pain | 35 (3%) 25 (2%) 9 (<1%) | 2 (<1%) 0 1 (<1%) | 0 0 |
| Renal and urinary disorders | Very common Uncommon | Proteinuria Urinary tract hemorrhage | 135 (12%) | 32 (3%) | 0 |
| Reproductive system and breast disorders | | Menorrhagia Vaginal hemorrhage | 3 (<1%) | 0 | 0 |
| General disorders and | Uncommon Very common | Metrorrhagia Fatigue | 1 (<1%) 415 (36%) | 0 65 (6%) | 0 1 (<1%) |
| administration site conditions | Common Common | Mucosal inflammation Asthenia | 86 (7%) 82 (7%) | 5 (<1%) 20 (2%) | 0 1 (<1%) |
| | Common Common | Edema ^b Chest pain | 72 (6%) 18 (2%) | 1 (<1%) 2 (<1%) | 0 |
| | Uncommon Uncommon | Chills Mucous membrane disorder | 4 (<1%) | 0 0 | 0 |
| Investigations | Very common | Alanine aminotransferase increased Incremento de aspartano | 246 (21%) | 84 (7%) 51 (4%) | 14 (1%) |
| | | | | | 10 (< 170) |
| | Common | aminotransferasa | | | 0 |
| | Common Common | | 96 (8%) 61 (5%) 55 (5%) | 7 (<1%) 6 (<1%) 3 (<1%) | |

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Common

Common

Common

Common

Common

Uncommon Uncommon

Uncommon

Uncommon

b Edema, peripheral edema, eye edema, localized edema and face edema c Dysgeusia, ageusia and hypogeusia d White cell count decrease, neutrophil count decrease, and leukocyte count decrease

decrease Blood thyroid stimulating hormoneincrease

Amylase increase

Gamma-glutamyltransf erase

increase Blood pressure increase Blood urea increase

Abnormal liver function test

Liver enzyme increase Blood glucose decrease

Prolonged electrocardiogram

QT

Transaminase increase

Abnormal thyroid function test

Blood pressure diastolic incre<u>ase</u> Uncommon Blood pressure systolic increase 1(<1%) † Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and

36 (3%)

35 (3%)

31 (3%)

15 (1%)

12 (1%)

12 (1%)

7 (<1%)

7 (<1%)

0

7 (<1%)

9 (<1%)

2 (<1%)

1 (<1%)

6 (<1%)

4 (<1%)

2 (<1%)

1 (<1%)

0

4 (<1%)

0

1 (<1%)

1 (<1%)

0

0

Table 2: Treatment-related adverse reactions reported in STS studies (n=382)

patients of East Asian descent.

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. Neutropenia, thrombocytopenia and palmar-plantar erythrodysaethesia syndrome were observed more frequently in

| System Organ Class Frequency | Frequency (all grades) | Adverse reactions | All grades n (%) | Grade 3 n (%) | Grade 4 r (%) |
|---|----------------------------|---|-------------------------|--------------------|------------------|
| Infections and | (all grades) Common | Gingival infection | n (%) 4 (<1%) | 0 | 0 |
| Infestations Neoplasms benign, | Very common | Tumor pain | 121 32%) | 32 (8%) | 0 |
| malignant and | very continion | rumor pain | 121 3270) | 32 (670) | U |
| unspecified (incl cysts and polyps) | | | | | |
| Blood and lymphatic | Common | Leukopenia | 106 (44%) | 3 (1 %) | 0 |
| system disorders | Common | Thrombocytopenia | 86 (36%) | 7 (3 %) | 2 (<1%) |
| | Common Uncommon | Neutropenia Thrombotic microangiopathy | 79 (33%) 1 (<1%) | 10 (4%) | 0 |
| | | (including thrombotic | | | |
| | | thrombocytopenic purpura and hemolytic uraemic | | | |
| For the code of the code of | C | syndrome) | 10 (50/) | | |
| Endocrine disorders Metabolism and nutrition | Common Very common | Hypothyroidism Appetite decrease ^e | 18 (5%) 108 (28%) | 12 (3%) | 0 |
| disorders | Very common | Hypoalbuminemia ^f | 81 (34%) | 2 (<1%) | 0 |
| | Common Uncommon | Dehydration Hypomagnesemia | 4 (1%) 1 (<1%) | 2 (1%) | 0 |
| Psychiatric disorders | Common | Insomnia | 5 (1%) | 1 (<1%) | 0 |
| Nervous system disorders | Very common Very common | Dysgeusia ^c Headache | 79 (21%) 54 (14%) | 2 (<1%) | 0 |
| | Common | Peripheral sensory neuropathy | 30 (8%) | 1 (<1%) | 0 |
| | Common Uncommon | Dizziness Somnolence | 15 (4%) 3 (<1%) | 0 | 0 |
| | Uncommon | Paresthesia | 1 (<1%) | 0 | 0 |
| Eyes disorders | Uncommon Uncommon | Cerebral infarction Blurred vision | 1 (<1%) 15 (4%) | 0 | 1 (<1%) 0 |
| Cardiac disorders | Common | Cardiac dysfunction ⁹ | 21 (5%) | 3 (<1%) | 1 (<1%) |
| | Common Common | Left ventricular dysfunction Bradycardia | 13 (3%) 4 (1%) | 3 (<1%) | 0 |
| | Uncommon | Myocardial infarction | 1 (<1%) | 0 | 0 |
| Vascular disorders | Very common Common | Hypertension Venous thromboembolic | 152 (40%) 13 (3%) | 26 (7%) 4 (1%) | 0 5 (1%) |
| | | event ^d | | | |
| | Common Common | Hot flush Flushing | 12 (3%) 4 (1%) | 0 | 0 |
| | Uncommon | Hemorrhage | 2 (<1%) | 1 (<1%) | 0 |
| Respiratory, thoracic and mediastinal disorders | Common | Epistaxis | 22 (6%) | 0 | 0 |
| mediastinal disorders | Common Common | Dysphonia Dyspnea | 20 (5%) 14 (4%) | 3 (<1%) | 0 |
| | Common | Cough | 12 (3%) | 0 | 0 |
| | Common Common | Pneumothorax Hiccups | 7 (2%) 4 (1%) | 2 (<1%) | 1 (<1%) |
| | Common | Pulmonary hemorrhage | 4 (1%) | 1 (<1%) | 0 |
| | Uncommon Uncommon | Oropharyngeal pain Bronchial hemorrhage | 3 (<1%) 2 (<1%) | 0 | 0 |
| | Uncommon | Rhinorrhea | 1 (<1%) | 0 | 0 |
| Gastrointestinal | Uncommon Very common | Hemoptysis Diarrhea | 1 (<1%) 174 (46%_) | 0 17 (4%) | 0 |
| disorders | Very common | Nausea | 167 (44%) | 7 (2%) | 0 |
| | Very common Very common | Vomiting Abdominal pain ^a | 96 (25%) 55 (14%) | 8 (2%) 15 (1%) | 0 |
| | Very common | Stomatitis | 41 (11%) | 1 (<1%) | 0 |
| | Common Common | Abdominal distension Dry mouth | 16 (4%) 14 (4%) | 2 (1%) | 0 |
| | Common | Dyspepsia | 12 (3%) | 0 | 0 |
| | Common Common | Mouth hemorrhage Flatulence | 5 (1%) 5 (1%) | 0 | 0 |
| | Common | Anal hemorrhage | 4 (1%) | 0 | 0 |
| | Uncommon Uncommon | Gastrointestinal hemorrhage Rectal hemorrhage | 2 (<1%) | 0 | 0 |
| | Uncommon | Enterocutaneous fistula | 1 (<1%) | 1 (<1%) | 0 |
| | Uncommon | Gastric hemorrhage | 1 (<1%) | 0 | 0 |
| | Uncommon Uncommon | Malena Esophageal hemorrhage | 2 (<1%) | 0 | 0 1 (<1%) |
| | Uncommon | Peritonitis | 1 (<1%) | 0 | 0 |
| | Uncommon Uncommon | Retroperitoneal hemorrhage Upper gastrointestinal | 1 (<1%) | 1 (<1%) 1 (<1%) | 0 |
| | | hemorrhage | | | |
| Hepatobiliary disorders | Uncommon Uncommon | Ileal perforation Abnormal hepatic function | 1 (<1%) 2 (<1%) | 0 | 1 (<1%) |
| Skin and subcutaneous | Very common | Hair colour change | 93 (24%) | Ů | 0 |
| disorders | Very common Very common | Skin hypopigmentation Exfoliative rash | 80 (21%) 52 (14%) | 2 (<1%) | 0 |
| | Common | Alopecia | 30 (8%) | 0 | 0 |
| | Common Common | Skin disorder ^c Dry skin | 26 (7%) 21 (5%) | 4 (1%) | 0 |
| | Common | Hyperhydrosis | 18 (5%) | 0 | 0 |
| | Common Common | Nail disorder Pruritus | 13 (3%) 11 (3%) | 0 | 0 |
| | Common | Erythema | 4 (1%) | 0 | 0 |
| | Uncommon | Skin ulcer Rash | 3 (<1%) 1 (<1%) | 1 (<1%) | 0 |
| | | Rash papular | 1 (<1%) | 0 | 0 |
| | | Photosensitivity reaction Palmar-plantar erythrodysaes- | 1 (<1%) | 0 | 0 |
| | | thesia syndrome | 2 (<1%) | | |
| Musculoskeletal and | Common Common | Musculoskeletal pain Myalgia | 35 (9%) 28 (7%) | 2 (<1%) 2 (<1%) | 0 |
| connective tissue disorders | Common | Myalgia Muscle spasm | 8 (2%) | ∠ (<1%) | U |
| Renal and urinary | Uncommon | Arthralgia Proteinuria | 2 (<1%) | 0 | 0 |
| Renal and urinary disorders | Uncommon | Proteinuria | 2 (<1%) | _ ' | U |
| Reproductive system and | | Vaginal hemorrhage | 3 (<1%) | 0 | 0 |
| breast disorders General disorders and administration site conditions | Uncommon Very common | Menorrhagia Fatigue | 1 (<1%) 178 (47%) | 0 34 (9%) | 0 1 (<1%) |
| | Common | Edema ^b | 18 (5%) | 1 (<1%) | 0 |
| | Common Common | Chest pain Chills | 12 (3%) 10 (3%) | 4 (1%) | 0 |
| | Uncommon | Mucosal inflammation ^e | 1 (<1%) | 0 | 0 |
| Investigations h | Uncommon Very common | Asthenia Weight loss | 1 (<1% 86 (23%) | 0 5 (<1%) | 0 |
| csugudons | Common | Ear, nose and throat examination abnormal ^e | 29 (8%) | 4 (1%) | 0 |
| | Common | Alanine aminotransferase increase | 8 (2%) | 4 (1%) | 2 (<1%) |
| | Common | Abnormal blood cholesterol | 6 (2%) | 0 2 (< 196) | 0 2 (<1%) |
| | Common | Aspartate aminotransferase increased | 5 (1%) | 2 (<1%) | ∠(<1%) |
| | Common | Gamma-glutamyltransferase | 4 (1%) | 0 | 3 (<1%) |
| | | increase | | | |

^a Abdominal pain, upper abdominal pain and gastrointestinal pain ^b Edema, peripheral edema and eyelid edema

The following terms have been combined:

^cThe majority of these cases were Palmar-plantar erythrodysesthesia syndrome ${}^{\rm d} \text{Venous thromboembolic events} - \text{includes deep vein thrombosis, pulmonary embolism} \text{ and thrombosis terms}$ The majority of these cases describe mucositis

Uncommon

Uncommon

Uncommon

Frequency is based on laboratory value tables from VEG110727 (N=240). These were reported as adverse events less frequently by investigators than as indicated by laboratory value tables. ${}^{
m g}$ Cardiac dysfunction events – includes left ventricular dysfunction, cardiac failure and restrictive cardiomyopa-

Blood bilirubin increase

Aspartate aminotransferase

Alanine aminotransferase Platelet count decreased

Prolonged electrocardiogram

QT

2 (<1%)

2 (<1%)

1 (<1%)

2 (<1%)

1 (<1%)

0

Prequency is based on adverse events reported by investigators. Laboratory abnormalities were reported as adverse events less frequently by investigators than as indicated by laboratory value tables. Preclinical safety data

The preclinical safety profile of pazopanib was assessed in mice, rats, rabbits, and monkeys. In repeated dose

studies in rodents, effects on a variety of tissues (bone, teeth, nail bed, reproductive organs, hematologic tissues, kidney, and pancreas) appear to be related to the pharmacology of VEGFR inhibition and / or the disruption of VEGF signaling pathways, with most of the effects occurring at plasma exposure levels below to those observed

clinically. Other observed effects included body weight loss, diarrhea and / or morbidity that were either secondary to local gastrointestinal effects caused by high drug exposure to the local mucosa (monkeys) or pharmacological effects (rodents). Proliferative liver lesions (eosinophil foci and adenoma) were observed in female mice at exposures 2.5 times the human exposure based on AUC. In juvenile toxicity studies when pre-weaning rats were dosed from day 9 postpartum through to day 14 postpartum, pazopanib caused deaths and abnormal development / maturation in the kidney, lung, liver and heart at doses approximately 0.1 times the clinical exposure based on AUC in adult humans. When post-weaning rats were dosed from day 21 postpartum to day 62 postpartum, toxicological findings were like

are at increased risk for bone and teeth effects as compared to adults, as these changes, including inhibition of growth (shortened limbs), fragile bones and remodeling of teeth, were present in juvenile rats at ≥ 10 mg/kg/day (equal to approximately 0.1-0.2 times the clinical exposure based on AUC in adult humans). Reproductive, fertility and teratogenic effects Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female

fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, decreased fetal body

adult rats at comparable exposures. Human pediatric patients

weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC. Genotoxicity Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic

in the Ames assay but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay. <u>Carcinogenicity</u> Carcinogenicity studies have not been performed with pazopanib.

Pazopanib doses up to 2000 mg have been evaluated in clinical studies. Grade 3 fatigue (dose-limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2000 mg and 1000 mg daily, respectively.

There is no specific antidote for overdose with pazopanib and treatment of overdose should consist of general supportive measures. Hemodialysis is not expected to increase the elimination of PACHTOR since pazopanib is not significantly excreted via the kidneys and is highly bound to plasma proteins.

HOSPITAL A. POSADAS PHONE NBR. (011)4654-6648/4658-7777

IN THE EVENT OF AN OVERDOSE, GO TO THE NEAREST HOSPITAL OR CONTACT THE POISON CENTERS: HOSPITAL DE PEDIATRIA RICARDO GUTIERREZ

PHONE NBR. (0221)451-5555

PRESENTATION: Package containing 30 film-coated tablets

PHONE NBR. (011) 4962-6666/2247

Store under 30 °C of temperature

STORAGE:

KEEP OUT OF THE REACH OF CHILDREN

THIS MEDICINE SHOULD ONLY BE USED UNDER STRICT MEDICAL CONTROL AND SURVEILLANCE AND CANNOT BE REPEATED WITHOUT A NEW PRESCRIPTION. MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH.

TECHNICAL DIRECTOR: Natalia Carolina Alonso, RPh

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CENTRO DE ASISTENCIA TOXICOLOGICA DE LA PLATA

CERTIFICATE No:57.484

serious adverse reactions from all pazopanib clinical studies). The following terms have been combined: a Abdominal pain, upper abdominal pain and lower abdominal pain