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For use in india only

MSN

Pazopanib Tablets 200 mg and 400 mg

Pazolong

पैज़ोलॉन्ग

To be sold by retail on the prescription of Oncologist only

WARNING: HEPATOTOXICITY

Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended

PRESCRIBING INFORMATION

1. GENERIC NAME

Pazopanib Tablets 200 mg and 400 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pazopanib Tablets 200
Each Film Coated Tablet Contains
Pazopanib Hydrochloride
Equivalent to Pazopanib....200 mg
Colours : Titanium Dioxide IP,
Ferric Oxide Red USP-NF

Pazopanib Tablets 400
Each Film Coated Tablet Contains
Pazopanib Hydrochloride
Equivalent to Pazopanib....400 mg
Colours : Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Pazopanib is available as a 200 mg and 400 mg tablets

4. CLINICAL PARTICULARS

4.1. Indications

Pazopanib is indicated for the treatment of patients with advanced renal cell carcinoma.

Pazopanib is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.

4.2. Posology ad Method of Administration

The recommended dosage of Pazopanib is 800 mg (four 200 mg tablets) orally once daily without food (at least 1 hour before or 2 hours after a meal) until disease progression or unacceptable toxicity. The dosage should be modified for hepatic impairment and in patients taking certain concomitant drugs.

Swallow tablets whole. Do not crush tablets due to the potential for increased rate of absorption, which may affect systemic exposure

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

Dosage Modifications for Adverse Reactions

Table 1 summarizes the recommended dose reductions.

Table 1. Recommended Dose Reductions of Pazopanib for Adverse Reactions

Dose Reduction	For Renal Cell Carcinoma	For Soft Tissue Sarcoma
First	400 mg orally once daily	600 mg orally once daily
Second	200 mg orally once daily	400 mg orally once daily

Permanently discontinue Pazopanib in patients unable to tolerate the second dose reduction.

Table 2 summarizes the recommended dosage modifications for adverse reactions.

Table 2. Recommended Dosage Modifications of Pazopanib for Adverse Reactions

Adverse reaction	Severity	Dosage
Hepatic Toxicity	Isolated ALT elevations between 3 × ULN and 8 × ULN	Continue and monitor liver function weekly until ALT returns to Grade 1 or baseline.
	Isolated ALT elevations of > 8 × ULN	Withhold until improvement to Grade 1 or baseline. If the potential benefit for resuming treatment with PAZOPANIB is considered to outweigh the risk for hepatotoxicity, then resume at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks. Permanently discontinue if ALT elevations > 3 × ULN recur despite dose reduction(s).
Left Ventricular Systolic Dysfunction	Symptomatic or Grade 3	Withhold until improvement to Grade < 3. Resume treatment based on medical judgement.
	Grade 4	Permanently discontinue.
Hemorrhagic Events	Grade 2	Withhold until improvement to Grade ≤ 1. Resume at reduced dose. Permanently discontinue if Grade 2 recurs after dose interruption and reduction.
	Grade 3 or 4	Permanently discontinue
Arterial Thromboembolic Events	Any grade	Permanently discontinue
Venous Thromboembolic Events	Grade 3	Withhold Pazopanib and resume at same dose if managed with appropriate therapy for at least one week.
	Grade 4	Permanently discontinue
Thrombotic Microangiopathy	Any grade	Permanently discontinue
Gastrointestinal Perforation	Any grade	Permanently discontinue
Gastrointestinal Fistula	Grade 2 or 3	Withhold and resume based on medical judgement
	Grade 4	Permanently discontinue
Interstitial Lung Disease	Any grade	Permanently discontinue
Posterior Reversible Encephalopathy Syndrome	Any grade	Permanently discontinue
Hypertension	Grade 2 or 3	Reduce dose (see Table 1) and initiate or adjust anti- hypertensive therapy. Permanently discontinue if hypertension remains Grade 3 despite dose reduction(s) and adjustment of anti- hypertensive therapy.
	Grade 4 or hypertensive crisis	Permanently discontinue
Proteinuria	24-hour urine protein ≥ 3 grams	Withhold until improvement to Grade ≤ 1. Resume at a reduced dose. Permanently discontinue if 24-hour urine protein ≥ 3 grams does not improve or recurs despite dose reductions.
	Confirmed nephrotic syndrome	Permanently discontinue

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal

Dosage modifications for Hepatic impairment

Moderate and Severe Hepatic Impairment

In patients with moderate hepatic impairment [total bilirubin > 1.5 to 3 × upper limit of normal (ULN) and any alanine aminotransferase (ALT) value], consider alternatives to Pazopanib. If Pazopanib is used in patients with moderate hepatic impairment, reduce the Pazopanib dose to 200 mg orally once daily.

Pazopanib is not recommended in patients with severe hepatic impairment

Dosage Modifications for Drug Interactions

Strong CYP3A4 Inhibitors

Avoid concomitant use of strong CYP3A4 inhibitors by use of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. If co-administration of a strong

CYP3A4 inhibitor is warranted; reduce the dose of Pazopanib to 400 mg.

Strong CYP3A4 Inducers

Avoid concomitant use of strong CYP3A4 inducers by use of an alternate concomitant medication with no or minimal enzyme induction potential. Pazopanib is not recommended in patients who cannot avoid chronic use of strong CYP3A4 inducers.

Gastric Acid-Reducing Agents

Avoid concomitant use of gastric acid-reducing agents. If concomitant use of a gastric acid-reducing agent cannot be avoided, consider short-acting antacid in place of proton pump inhibitors (PPIs) and H2-receptor antagonists. Separate short-acting antacid and Pazopanib dosing by several hours.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.

4.4. Special Warnings and Precautions for Use

Hepatic Toxicity

Hepatotoxicity, manifested as increases in ALT, aspartate aminotransferase (AST) and bilirubin, occurred in patients who received Pazopanib. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment; 92% of all transaminase elevations of any grade occurred in the first 18 weeks.

Monitor liver tests at baseline; at Weeks 3, 5, 7, and 9; at Month 3 and Month 4; and then periodically as clinically indicated. Increase to weekly monitoring for patients with elevated ALT until ALT returns to Grade 1 or baseline. Withhold Pazopanib and resume at reduced dose with continued weekly monitoring for 8 weeks, or permanently discontinue with weekly monitoring until resolution based on severity of hepatotoxicity.

Gilbert's Syndrome

Pazopanib is a uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. In patients with only a mild indirect hyperbilirubinemia known as Gilbert's syndrome, manage elevation in ALT > 3 × ULN per the recommendations outlined for isolated ALT elevations.

Concomitant Use of Simvastatin

Concomitant use of Pazopanib and simvastatin increases the risk of ALT elevations. Insufficient data are available to assess the risk of concomitant administration of alternative statins and Pazopanib.

QT Prolongation and Torsades de Pointes

Monitor patients who are at significant risk of developing QTc prolongation, including patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant preexisting cardiac disease. Monitor ECG and electrolytes (e.g., calcium, magnesium, potassium) at baseline and as clinically indicated. Correct hypokalemia, hypomagnesemia, and hypocalcaemia prior to initiating Pazopanib and during treatment.

Cardiac Dysfunction

Cardiac dysfunction, including decreased left ventricular ejection fraction (LVEF) and congestive heart failure, occurred in patients who received Pazopanib.

Monitor blood pressure and manage as appropriate. Monitor for clinical signs or symptoms of congestive heart failure. Conduct baseline and periodic evaluation of LVEF in patients at risk of cardiac dysfunction, including previous anthracycline exposure. Withhold or permanently discontinue Pazopanib based on severity of cardiac dysfunction.

Hemorrhagic Events

Pazopanib has not been studied in patients who have a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months. Withhold Pazopanib and resume at reduced dose or permanently discontinue based on severity of hemorrhagic events.

Arterial Thromboembolic Events

Pazopanib has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months. Permanently discontinue Pazopanib in case of an arterial thromboembolic event.

Venous Thromboembolic Events

Venous thromboembolic events (VTEs), including venous thrombosis and fatal pulmonary embolus (PE), occurred in patients who received Pazopanib.

Monitor for signs and symptoms of VTE and PE. Withhold Pazopanib and then resume at same dose or permanently discontinue based on severity of VTE.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), occurred in clinical trials of Pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Pazopanib is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of Pazopanib. Improvement of TMA was observed after treatment was discontinued.

Monitor for signs and symptoms of TMA. Permanently discontinue Pazopanib in patients developing TMA. Manage as clinicaly indicated.

Gastrointestinal Perforation and Fistula

Monitor for signs and symptoms of gastrointestinal perforation or fistula. Withhold Pazopanib in case of Grade 2 or 3 gastrointestinal fistula and resume based on medical judgement. Permanently discontinue Pazopanib in case of gastrointestinal perforation or Grade 4 gastrointestinal fistula.

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis, which can be fatal, has been reported with Pazopanib across clinical trials. ILD/pneumonitis occurred in 0.1% of patients treated with Pazopanib.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Permanently discontinue Pazopanib in patients who develop ILD or pneumonitis.

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) has been reported in patients who received Pazopanib and may be fatal. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. Confirm diagnosis of PRES by magnetic resonance imaging.

Permanently discontinue Pazopanib in patients who develop PRES.

Hypertension

Hypertension (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg) and hypertensive crisis were observed in patients treated with Pazopanib.

Do not initiate Pazopanib in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Pazopanib. Monitor blood pressure as clinically indicated and initiate and adjust antihypertensive therapy as appropriate. Withhold and then dose reduce Pazopanib or permanently discontinue based on severity of hypertension.

Risk of Impaired Wound Healing

Impaired wound healing complications can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signalling pathway. Therefore, Pazopanib has the potential to adversely affect wound healing.

Withhold Pazopanib at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Pazopanib after resolution of wound healing complications has not been established.

Hypothyroidism

Monitor thyroid tests at baseline, during treatment and as clinically indicated and manage hypothyroidism as appropriate.

Proteinuria

Perform baseline and periodic urinalysis during treatment with follow up measurement of 24-hour urine protein as clinically indicated. Withhold Pazopanib then resume at a reduced dose or permanently discontinue based on severity of proteinuria. Permanently discontinue in patients with nephrotic syndrome.

Tumor Lysis Syndrome

Cases of tumour lysis syndrome (TLS), including fatal cases, have been reported in RCC and STS patients treated with Pazopanib. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis, and treat as clinically indicated.

Infection

Serious infections (with or without neutropenia), including some with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of Pazopanib for serious infections.

Increased Toxicity With Other Cancer Therapy

Pazopanib is not indicated for use in combination with other agents. Clinical trials of Pazopanib in combination with pemetrexed and lapatinib were terminated early due to increased toxicity and mortality. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.

Increased Toxicity in Developing Organs

The safety and effectiveness of Pazopanib in pediatric patients have not been established. Pazopanib is not indicated for use in pediatric patients. Based on its mechanism of action, Pazopanib may have severe effects on organ growth and maturation during early postnatal development. Administration of Pazopanib to juvenile rats < 21 days old resulted in toxicity to the lungs, liver, heart, and kidney and in death at doses significantly lower than the clinically recommended dose or doses tolerated in older animals. Pazopanib may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Pazopanib can cause foetal harm when administered to a pregnant woman. Administration of Pazopanib to pregnant rats and rabbits during the period of organogenesis resulted in maternal toxicity, teratogenicity, and abortion at systemic exposures lower than that observed at the maximum recommended human dose (MRHD) of 800 mg (based on area under the curve [AUC]).

Advise pregnant women of the potential risk to a foetus. Advise females of reproductive potential to use effective contraception during treatment with Pazopanib and for at least 2 weeks following the final dose. Advise males (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with Pazopanib and for at least 2 weeks after the last dose.

4.5. Drug Interactions

Effect of Other Drugs on Pazopanib

Strong CYP3A4 Inhibitors

Co-administration of Pazopanib with strong inhibitors of CYP3A4 increases Pazopanib concentrations. Avoid co-administration of Pazopanib with strong CYP3A4 inhibitors and consider an alternate concomitant medication with no or minimal enzyme inhibition potential. If co-administration of a strong CYP3A4 inhibitor cannot be avoided, reduce the dose of Pazopanib.

Strong CYP3A4 Inducers

Coadministration of strong CYP3A4 inducers may decrease plasma pazopanib concentrations. Consider an alternate concomitant medication with no or minimal enzyme induction potential. Pazopanib is not recommended if chronic use of strong CYP3A4 inducers cannot be avoided.

Transporters

Co-administration of strong inhibitors of P-gp or BCRP may increase pazopanib concentrations. Avoid concomitant use of Pazopanib with strong inhibitors of P-gp or BCRP. Consider selection of alternative concomitant medicinal products with no or minimal potential to inhibit P-gp or BCRP.

Effects of Pazopanib on Other Drugs

CYP Substrates

Coadministration of Pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 may result in inhibition of the metabolism of these products and create the potential for serious adverse reactions. The concomitant use of Pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

Concomitant Use with Simvastatin

Concomitant use of Pazopanib with simvastatin increases the incidence of ALT elevations. Across clinical trials of Pazopanib as a single agent, ALT > 3 × ULN was reported in 126/895 (14%) of patients who did not use statins compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, increase to weekly monitoring of liver function as recommended. Withhold Pazopanib and resume at reduced dose, or permanently discontinue based on severity of hepatotoxicity. Insufficient data are available to assess the risk of concomitant administration of alternative statins and Pazopanib.

Concomitant Use With Gastric Acid-Reducing Agents

Concomitant use of Pazopanib with esomeprazole, a PPI, decreased the exposure of Pazopanib. Avoid concomitant use of Pazopanib with gastric acid-reducing agents. If concomitant administration with a gastric acid-reducing agent cannot be avoided, consider short-acting antacids in place of PPIs and H2-receptor antagonists. Separate short-acting antacid and Pazopanib dosing by several hours to avoid a reduction in Pazopanib exposure.

Drugs That Prolong the QT Interval

Pazopanib is associated with QTc interval prolongation. Avoid co-administration of Pazopanib with drugs known to prolong the QT/QTc interval.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Based on animal reproduction studies and its mechanism of action, Pazopanib can cause fetal harm when administered to a pregnant woman. There are no available data on Pazopanib use in pregnant women to evaluate for a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of Pazopanib to pregnant rats and rabbits throughout organogenesis resulted in teratogenicity, and abortion at systemic exposures lower than that observed at the MRHD of 800 mg/day (based on AUC). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes.

Lactation

There is no data on the presence of Pazopanib or its metabolites in human milk or their effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Pazopanib and for 2 weeks after the final dose.

Lactation

There is no data on the presence of Pazopanib or its metabolites in human milk or their effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Pazopanib and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pazopanib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to starting treatment with Pazopanib.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Pazopanib and for at least 2 weeks after the last dose.

Males

Advise males (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with Pazopanib and for at least 2 weeks after the last dose.

Infertility

Based on findings from animal studies, Pazopanib may impair fertility in females and males of reproductive potential while receiving treatment.

Pediatric Use

The safety and effectiveness of Pazopanib in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness of Pazopanib were observed between patients aged ≥ 65 years and younger patients.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment. Pazopanib has not been studied in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (either total bilirubin ≤ ULN and ALT > ULN or bilirubin > 1 to 1.5 × ULN and any ALT value). Pazopanib is not recommended in patients with moderate (total bilirubin > 1.5 to 3 ×ULN and any ALT value) and severe (total bilirubin > 3 × ULN and any ALT value) hepatic impairment

4.7. Effects on Ability to Drive and Use Machines

Pazopanib 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 should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

4.8. Undesirable Effects

Tabulated list of adverse reactions

Table 2 Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and Infestations	Common	Infections (with or without neutropenia)†	not known	not known	not known
	Uncommon	Gingival infection	1 (<1%)	0	0
		Infectious peritonitis	1 (<1%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Tumour pain	1 (<1%)	1 (<1%)	0
Blood and lymphatic system disorders	Common	Thrombocytopenia	80 (7%)	10 (<1%)	5 (<1%)
		Neutropenia	79 (7%)	20 (2%)	4 (<1%)
		Leukopenia	63 (5%)	5 (<1%)	0
	Uncommon	Polycythaemia	6 (0.03%)	1	0
	Rare	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†	not known	not known	not known
Endocrine disorders	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
Metabolism and nutrition disorders	Very common	Decreased appetite[e]	317 (28%)	14 (1%)	0
	Common	Hypophosphataemia	21 (2%)	7 (<1%)	0
		Dehydration	16 (1%)	5 (<1%)	0
	Uncommon	Hypomagnesaemia	10 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not known	not known
Psychiatric disorders	Common	Insomnia	30 (3%)	0	0
Nervous system disorders	Very common	Dysgeusia[c]	254 (22%)	1 (<1%)	0
		Headache	122 (11%)	11 (<1%)	0
	Common	Dizziness	55 (5%)	3 (<1%)	1 (<1%)
		Lethargy	30 (3%)	3 (<1%)	0
		Paraesthesia	20 (2%)	2 (<1%)	0
		Peripheral sensory neuropathy	17 (1%)	0	0
	Uncommon	Hypoaesthesia	8 (<1%)	0	0
		Transient ischaemic attack	7 (<1%)	4 (<1%)	0
		Somnolence	3 (<1%)	1 (<1%)	0
		Cerebrovascular accident	2 (<1%)	1 (<1%)	1 (<1%)
		Ischaemic stroke	2 (<1%)	0	1 (<1%)
	Rare	Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome†	not known	not known	not known
Eye disorders	Common	Vision blurred	19 (2%)	1 (<1%)	0
	Uncommon	Retinal detachment†	1 (<1%)	1 (<1%)	0
		Retinal tear†	1 (<1%)	1 (<1%)	0
		Eyelash discolouration	4 (<1%)	0	0
Cardiac disorders	Uncommon	Bradycardia	6 (<1%)	0	0
		Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)
		Cardiac dysfunction[f]	4 (<1%)	1 (<1%)	0
		Myocardial ischaemia	3 (<1%)	1 (<1%)	0
Vascular disorders	Very common	Hypertension	473 (41%)	115 (10%)	1 (<1%)
	Common	Hot flush	16 (1%)	0	0
		Venous thromboembolic event[g]	13 (1%)	6 (<1%)	7 (<1%)
		Flushing	12 (1%)	0	0
	Uncommon	Hypertensive crisis	6 (<1%)	0	2 (<1%)
		Haemorrhage	1 (<1%)	0	0
	Not known	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	50 (4%)	1 (<1%)	0
		Dysphonia	48 (4%)	0	0
		Dyspnoea	42 (4%)	8 (<1%)	1 (<1%)
		Haemoptysis	15 (1%)	1 (<1%)	0
	Uncommon	Rhinorrhoea	8 (<1%)	0	0
		Pulmonary haemorrhage	2 (<1%)	0	0
		Pneumothorax	1 (<1%)	0	0
	Rare	Interstitial lung disease/pneumonitis†	not known	not known	not known
Gastrointestinal disorders	Very common	Diarrhoea	614 (53%)	65 (6%)	2 (<1%)
		Nausea	386 (34%)	14 (1%)	0
		Vomiting	225 (20%)	18 (2%)	1 (<1%)
		Abdominal pain[a]	139 (12%)	15 (1%)	0
	Common	Stomatitis	96 (8%)	4 (<1%)	0
		Dyspepsia	83 (7%)	2 (<1%)	0
		Flatulence	43 (4%)	0	0
		Abdominal distension	36 (3%)	2 (<1%)	0
		Mouth ulceration	28 (2%)	3 (<1%)	0
		Dry mouth	27 (2%)	0	0
	Uncommon	Pancreatitis	8 (<1%)	4 (<1%)	0
		Rectal haemorrhage	8 (<1%)	2 (<1%)	0
		Haematochezia	6 (<1%)	0	0
		Gastrointestinal haemorrhage	4 (<1%)	2 (<1%)	0
		Melaena	4 (<1%)	1(<1%)	0
		Frequent bowel movements	3 (<1%)	0	0
		Anal haemorrhage	2 (<1%)	0	0
		Large intestine perforation	2 (<1%)	1 (<1%)	0
		Mouth haemorrhage	2 (<1%)	0	0
		Upper gastrointestinal haemorrhage	2 (<1%)	1 (<1%)	0
		Enterocutaneous fistula	1 (<1%)	0	0
		Haematemesis	1 (<1%)	0	0
		Haemorrhoidal haemorrhage	1 (<1%)	0	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
		Oesophageal haemorrhage	1 (<1%)	0	0
		Retroperitoneal haemorrhage	1 (<1%)	0	0
Hepatobiliary disorders	Common	Hyperbilirubinaemia	38 (3%)	2 (<1%)	1 (<1%)
		Hepatic function abnormal	29 (3%)	13 (1%)	2 (<1%)
		Hepatotoxicity	18 (2%)	11(<1%)	2 (<1%)
		Uncommon	Jaundice	3 (<1%)	1 (<1%)
		Drug induced liver injury	2 (<1%)	2 (<1%)	0
		Hepatic failure†	1 (<1%)	0	1 (<1%)
Skin and subcutaneous disorders	Very common	Hair colour change	404 (35%)	1 (<1%)	0
		Palmar-plantar erythrodysaesthesia syndrome	206 (18%)	39 (3%)	0
		Alopecia	130 (11%)	0	0
		Rash	129 (11%)	7 (<1%)	0
	Common	Skin hypopigmentation	52 (5%)	0	0
		Dry skin	50 (4%)	0	0
		Pruritus	29 (3%)	0	0
		Erythema	25 (2%)	0	0
		Skin depigmentation	20 (2%)	0	0
		Hyperhidrosis	17 (1%)	0	0
	Uncommon	Nail disorders	11 (<1%)	0	0
		Skin exfoliation	10 (<1%)	0	0
		Photosensitivity reaction	7 (<1%)	0	0
		Rash erythematous	6 (<1%)	0	0
		Skin disorder	5 (<1%)	0	0
		Rash macular	4 (<1%)	0	0
		Rash pruritic	3 (<1%)	0	0
		Rash vesicular	3 (<1%)	0	0
		Pruritus generalised	2 (<1%)	1 (<1%)	0
		Rash generalised	2 (<1%)	0	0
		Rash papular	2 (<1%)	0	0
		Plantar erythema	1 (<1%)	0	0
Musculoskeletal and connective tissue disorders	Common	Arthralgia	48 (4%)	8 (<1%)	0
		Myalgia	35 (3%)	2 (<1%)	0
		Muscle spasms	25 (2%)	0	0
	Uncommon	Musculoskeletal pain	9 (<1%)	1 (<1%)	0
Renal and urinary disorders	Very Common	Proteinuria	135 (12%)	32 (3%)	0
	Uncommon	Haemorrhage urinary tract	1 (<1%)	0	0
Reproductive system and breast disorders	Uncommon	Menorrhagia	3 (<1%)	0	0
		Vaginal haemorrhage	3 (<1%)	0	0
		Metrorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	Very common	Fatigue	415 (36%)	65 (6%)	1 (<1%)
	Common	Mucosal inflammation	86 (7%)	5 (<1%)	0
		Asthenia	82 (7%)	20 (2%)	1 (<1%)
		Oedema[b]	72 (6%)	1 (<1%)	0
		Chest pain	18 (2%)	2 (<1%)	0
	Uncommon	Chills	4 (<1%)	0	0
		Mucous membrane disorder	1 (<1%)	0	0
Investigations	Very common	Alanine aminotransferase increased	246 (21%)	84 (7%)	14 (1%)
		Aspartate aminotransferase increased	211 (18%)	51 (4%)	10 (<1%)
	Common	Weight decreased	96 (8%)	7 (<1%)	0
		Blood bilirubin increased	61 (5%)	6 (<1%)	1 (<1%)
		Blood creatinine increased	55 (5%)	3 (<1%)	0
		Lipase increased	51 (4%)	21 (2%)	7 (<1%)
		White blood cell count decreased[d]	51 (4%)	3 (<1%)	0
		Blood thyroid stimulating hormone increased	36 (3%)	0	0
		Amylase increased	35 (3%)	7 (<1%)	0
		Gamma glutamyltransferase increased	31 (3%)	9 (<1%)	4 (<1%)
		Blood pressure increased	15 (1%)	2 (<1%)	0
		Blood urea increased	12 (1%)	1 (<1%)	0
		Liver function test abnormal	12 (1%)	6 (<1%)	1 (<1%)
	Uncommon	Hepatic enzyme increased	11 (<1%)	4 (<1%)	3 (<1%)
		Blood glucose decreased	7 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	7 (<1%)	2 (<1%)	0
		Transaminase increased	7 (<1%)	1 (<1%)	0
		Thyroid function test abnormal	3 (<1%)	0	0
		Blood pressure diastolic increased	2 (<1%)	0	0
		Blood pressure systolic increased	1 (<1%)	0	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
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

Table 3 Treatment-related adverse reactions reported in STS studies (n=382) or during post-marketing period

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and infestations	Common	Gingival infection	4 (1%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common	Tumour pain	121 (32%)	32 (8%)	0
Blood and lymphatic system disorders[f]	Very common	Leukopenia	106 (44%)	3 (1%)	0
		Thrombocytopenia	86 (36%	7 (3%)	2 (<1%)
		Neutropenia	79 (33%)	10 (4%)	0
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)	1 (<1%)	1 (<1%)	0
Endocrine disorders	Common	Hypothyroidism	18 (5%)	0	0
Metabolism and nutrition disorders	Very common	Decreased appetite	108 (28%)	12 (3%)	0
		Hypoalbuminemia[f]	81 (34%)	2 (<1%)	0
	Common	Dehydration	4 (1%)	2 (1%)	0
	Uncommon	Hypomagnesaemia	1 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not known	not known
Psychiatric disorders	Common	Insomnia	5 (1%)	1 (<1%)	0
Nervous system disorders	Very common	Dysgeusia[c]	79 (21%)	0	0
		Headache	54 (14%)	2 (<1%)	0
	Common	Peripheral sensory neuropathy	30 (8%)	1 (<1%)	0
		Dizziness	15 (4%)	0	0
	Uncommon	Somnolence	3 (<1%)	0	0
		Paresthesia	1 (<1%)	0	0
		Cerebral infarction	1 (<1%)	0	1 (<1%)
Eye disorders	Common	Vision blurred	15 (4%)	0	0
Cardiac disorders	Common	Cardiac dysfunction[g]	21 (5%)	3 (<1%)	1 (<1%)
		Left ventricular dysfunction	13 (3%)	3 (<1%)	0
		Bradycardia	4 (1%)	0	0
	Uncommon	Myocardial infarction	1 (<1%)	0	0
Vascular disorders	Very common	Hypertension	152 (40%)	26 (7%)	0
	Common	Venous thromboembolic eventd	13 (3%)	4 (1%)	5 (1%)
		Hot flush	12 (3%)	0	0
		Flushing	4 (1%)	0	0
	Uncommon	Haemorrhage	2 (<1%)	1 (<1%)	0
	Not known	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	22 (6%)	0	0
		Dysphonia	20 (5%)	0	0
		Dyspnoea	14 (4%)	3 (<1%)	0
		Cough	12 (3%)	0	0
		Pneumothorax	7 (2%)	2 (<1%)	1 (<1%)
		Hiccups	4 (1%)	0	0
		Pulmonary haemorrhage	4 (1%)	1 (<1%)	0
	Uncommon	Oropharyngeal pain	3 (<1%)	0	0
		Bronchial haemorrhage	2 (<1%)	0	0
		Rhinorrhoea	1 (<1%)	0	0
		Haemoptysis	1 (<1%)	0	0
	Rare	Interstitial lung disease/ pneumonitis†	not known	not known	not known
Gastrointestinal disorders	Very common	Diarrhoea	174 (46%)	17 (4%)	0
		Nausea	167 (44%)	8 (2%)	0
		Vomiting	96 (25%)	7 (2%)	0
		Abdominal pain[a]	55 (14%)	4 (1%)	0
		Stomatitis	41 (11%)	1 (<1%)	0
	Common	Abdominal distension	16 (4%)	2 (1%)	0
		Dry mouth	14 (4%)	0	0
		Dyspepsia	12 (3%)	0	0
		Mouth haemorrhage	5 (1%)	0	0
		Flatulence	5 (1%)	0	0
		Anal haemorrhage	4 (1%)	0	0
	Uncommon	Gastrointestinal haemorrhage	2 (<1%)	0	0
		Rectal haemorrhage	2 (<1%)	0	0
		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0
		Gastric haemorrhage	1 (<1%)	0	0
		Melaena	2 (<1%)	0	0
		Oesophageal haemorrhage	1 (<1%)	0	1 (<1%)
		Peritonitis	1 (<1%)	0	0
		Retroperitoneal haemorrhage	1 (<1%)	0	0
		Upper gastrointestinal haemorrhage	1 (<1%)	1 (<1%)	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
Hepatobiliary disorders	Uncommon	Hepatic function abnormal	2 (<1%)	0	1 (<1%)
	Not known	Hepatic failure*	not known	not known	not known
Skin and subcutaneous disorders	Very common	Hair colour change	93 (24%)	0	0
		Skin hypopigmentation	80 (21%)	0	0
		Exfoliative rash	52 (14%)	2 (<1%)	0
		Common	Alopecia	30 (8%)	0
		Skin disorder[c]	26 (7%)	4 (1%)	0
		Dry skin	21 (5%)	0	0
		Hyperhydrosis	18 (5%)	0	0
		Nail disorder	13 (3%)	0	0
		Pruritus	11 (3%)	0	0
		Erythema	4 (1%)	0	0
	Uncommon	Skin ulcer	3 (<1%)	1 (<1%)	0
		Rash	1 (<1%)	0	0
		Rash papular	1 (<1%)	0	0
		Photosensitivity reaction	1 (<1%)	0	0
		Palmar-plantar erythrodysaesthesia syndrome	2 (<1%)	0	0
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain	35 (9%)	2 (<1%)	0
		Myalgia	28 (7%)	2 (<1%)	0
		Muscle spasms	8 (2%)	0	0
	Uncommon	Arthralgia	2 (<1%)	0	0
Renal and urinary disorders	Uncommon	Proteinuria	2 (<1%)	0	0
Reproductive system and breast disorder	Uncommon	Vaginal haemorrhage	3 (<1%)	0	0
		Menorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	Very common	Fatigue	178 (47%)	34 (9%)	1 (<1%)
	Common	Oedema[b]	18 (5%)	1 (<1%)	0
		Chest pain	12 (3%)	4 (1%)	0
		Chills	10 (3%)	0	0
	Uncommon	Mucosal inflammation[e]	1 (<1%)	0	0
		Asthenia	1 (<1%)	0	0
Investigations[h]	Very common	Weight decreased	86 (23%)	5 (1%)	0
	Common	Ear, nose and throat examination abnormal[e]	29 (8%)	4 (1%)	0
		Alanine aminotransferase increased	8 (2%)	4 (1%)	2 (<1%)
		Blood cholesterol abnormal	6 (2%)	0	0
		Aspartate aminotransferase increased	5 (1%)	2 (<1%)	2 (<1%)
		Gamma glutamyltransferase increased	4 (1%)	0	3 (<1%)
	Uncommon	Blood bilirubin increased	2 (<1%)	0	0
		Aspartate aminotransferase	2 (<1%)	0	2 (<1%)
		Alanine aminotransferase	1 (<1%)	0	1 (<1%)
		Platelet count decreased	1 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	2 (<1%)	1 (<1%)	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
The following terms have been combined:
a Abdominal pain, abdominal pain upper and gastrointestinal pain
b Oedema, oedema peripheral and eyelid oedema
c The majority of these cases were Palmar-plantar erythrodysaesthesia syndrome
d Venous thromboembolic events – includes Deep vein thrombosis, Pulmonary embolism and Thrombosis terms
e The majority of these cases describe mucositis
f 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.
g Cardiac dysfunction events – includes Left ventricular dysfunction, Cardiac failure and Restrictive cardiomyopathy
h Frequency 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on +91- 40 38265227 **(Direct line); +91 7331134745 (WhatApp)**. By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose

Dose-limiting toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in1 of 3 patients dosed at 2,000 mg daily (2.5 times the recommended dose) and 1,000 mg daily (1.25 times the recommended dose), respectively.

Provide general supportive measures to manage an overdose. Hemodialysis is not expected to enhance the elimination of Pazopanib because Pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (Kit), interleukin-2 receptor-inducible T-cell kinase (Itk), lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-21 23 7 2Fms). *In vitro*, Pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit, and PDGFR-β receptors. *In vivo*, Pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

Pharmacodynamic effects

Increases in blood pressure have been observed and are related to steady-state trough plasma Pazopanib concentrations.

Cardiac Electrophysiology

The QT prolongation potential of Pazopanib was assessed in a randomized, blinded, parallel trial (N = 96) using moxifloxacin as a positive control. Pazopanib 800 mg orally under fasting conditions was administered on Days 2 to 8 and 1,600 mg was administered on Day 9 after a meal in order to increase exposure to Pazopanib and its metabolites. No large changes (i.e., > 20 msec) in QTc interval following exposure to Pazopanib were detected in this QT trial. The trial was not able to exclude small changes (< 10 msec) in QTc interval, because assay sensitivity below this threshold (< 10 msec) was not established in this trial.

5.2. Pharmacokinetic Properties

The recommended dosage of 800 mg once daily results in mean AUC of 1,037 mcg•h/mL and C of 58.1 mcg/mL. There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

Administration of a single 400-mg crushed tablet increased AUC by 46% and C by approximately 2-fold and decreased T by approximately 2 hours compared with administration of the whole tablet

Absorption

The median time to achieve peak concentrations was 2 to 4 hours after a dose.

Systemic exposure to Pazopanib is increased when administered with food. Administration of Pazopanib with a high-fat (approximately 50% fat) or low-fat (approximately 5% fat) meal results in an approximately 2-fold increase in AUC and C_{max}.

Distribution

Binding of Pazopanib to human plasma protein *in vivo* was > 99% with no concentration dependence over the range of 10 to 100 mcg/mL. *In vitro* studies suggest that Pazopanib is a substrate for P-gp and BCRP.

Metabolism

In vitro studies demonstrated that Pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

Elimination

Pazopanib has a mean half-life of 31 hours after administration of the recommended dose of 800 mg.

Excretion

Elimination is primarily via feces with renal elimination accounting for < 4% of the administered dose.

Specific Populations

Patients with Hepatic Impairment

Table 7 presents a comparison of the median steady-state C_{max} and the median AUC_{0-24h} values for patients with normal, mild, moderate and severe hepatic impairment.

The median steady-state of pazopanib C_{max} and AUC_{0-24h} after a once-daily dose of 800 mg in patients with mild impairment were in a similar range as the median steady-state C and median AUC in patients with no hepatic impairment.

The maximum tolerated pazopanib dose in patients with moderate hepatic impairment was 200 mg once daily. The median steady-state C_{max} and the median AUC_{0-24h} were approximately 43% and 29%, respectively, of the corresponding median values after administration of 800 mg once daily in patients with no hepatic impairment.

The median steady-state C_{max} and the median AUC_{0-24h} were approximately 18% and 15%, respectively, of the corresponding median values after administration of 800 mg once daily in patients with no hepatic impairment.

Drug Interactions Studies

Clinical Studies

Strong CYP3A4 Inhibitor: Coadministration of multiple doses of oral Pazopanib 400 mg with multiple doses of oral ketoconazole 400 mg (strong CYP3A4/P-gp inhibitor) resulted in a 1.7-fold increase in the AUC_{0-24h} and a 1.5-fold increase in the C_{max} of Pazopanib.

Weak CYP3A4 Inhibitor: Coadministration of 1,500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, P-gp, and BCRP, with Pazopanib 800 mg resulted in an approximately 50% to 60% increase in mean Pazopanib AUC_{0-24h} and C_{max}.

CYP1A2, CYP2C9 and CYP2C19 Substrates: Clinical studies, using Pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in patients with cancer.

CYP3A4, CYP2D6, and CYP2C8 Substrates: Coadministration of Pazopanib resulted in an increase of approximately 30% in the mean AUC and C of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Coadministration of PAZOPANIB 800 mg once daily and paclitaxel 80 mg/m (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively.

Gastric Acid-Reducing Agents: Coadministration of Pazopanib with esomeprazole, a PPI, decreased the exposure of Pazopanib by approximately 40% (AUC and C_{max}).

In Vitro Studies

In vitro studies with human liver microsomes showed that Pazopanib inhibited the activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human pregnane X receptor (PXR) assay.

In vitro studies also showed that pazopanib inhibits UGT1A1 and organic anion transporting polypeptide (OATP1B1) with IC s of 1.2 and 0.79 μM, respectively.

Pharmacogenomics

Pazopanib can increase serum total bilirubin levels. *In vitro* studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. A pooled pharmacogenetic analysis of 236 white patients who received Pazopanib showed that the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert's syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes.

6. NONCLINICAL PROPERTIES

6.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Pazopanib was evaluated in CD-1 mice, and Sprague-dawley rats. Administration of Pazopanib to mice for 2 years did not result in increased incidence of neoplasms at doses up to 100 mg/kg/day (approximately 1.4-fold the AUC at the MRHD of 800 mg/day). Administration of Pazopanib to rats for 2 years resulted in findings of duodenal adenocarcinoma in males at 30 mg/kg/day (approximately 0.3-fold the AUC at the MRHD of 800 mg/day) and in females at greater than or equal to 10 mg/kg/day (approximately 0.3-fold the AUC at the MRHD of 800 mg/day). The human relevance of these neoplastic findings is unclear.

Pazopanib did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

In an oral female fertility and early embryonic development study, female rats were administered Pazopanib at least 15 days prior to mating, and for 6 days after mating. Pazopanib did affect fertility in female rats. Reduced fertility, including increased preimplantation loss and early resorptions, were noted at dosages greater than or equal to 30 mg/kg/day (approximately 0.4-fold the AUC at the MRHD of 800 mg/day). Decreased corpora lutea and increased cysts were noted in mice given greater than or equal to 100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given greater than or equal to 300 mg/kg/day for 26 weeks (approximately 1.3 and 0.85-fold the AUC at the MRHD of 800 mg/day). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to 34 weeks (approximately 0.4-fold the AUC at the MRHD of 800 mg/day).

Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates and testicular sperm concentrations at doses greater than or equal to 3 mg/kg/day, epididymal sperm concentrations at doses greater than or equal to 30 mg/kg/day, and sperm motility at greater than or equal to 100 mg/kg/day following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at doses of greater than or equal to 30 mg/kg/day (approximately 0.35-fold the AUC at the MRHD of 800 mg/day); atrophy and degeneration of the testes with aspermia, hypospermia, and cribiform change in the epididymis was also observed at this dose in the 6-month toxicity studies in male rats.

7. PHARMACEUTICAL PARTICULARS

7.1. Incompatibilities

Not applicable.

7.2. Packing Information

30's Bottle pack

7.3. Storage and Handling Information

Do not store above 30°C

KEEP OUT OF REACH FOR CHILDREN.

8. PATIENT COUNSELING INFORMATION

Advise the patient to read the package insert.

- *Hepatic Toxicity*: Inform patients that periodic laboratory testing will be performed. Advise patients to report signs and symptoms of liver dysfunction to their healthcare provider right away.
- *QTc Prolongation and Torsades de Pointes*: Inform patients that ECG monitoring may be performed. Advise patients to inform their physicians of concomitant medications.
- *Interstitial Lung Disease/Pneumonitis*: Advise patients to report pulmonary signs or symptoms indicative of interstitial lung disease (ILD) or pneumonitis.
- *Cardiac Dysfunction*: Advise patients to report hypertension or signs and symptoms of congestive heart failure.
- *Hemorrhagic Events*: Advise patients to report unusual bleeding.
- *Arterial Thromboembolic Events*: Advise patients to report signs or symptoms of an arterial thrombosis.
- *Pneumothorax and Venous Thromboembolic Events*: Advise patients to report new onset of dyspnea, chest pain, or localized limb edema.
- *Posterior Reversible Encephalopathy Syndrome*: Advise patients to inform their doctor if they have worsening of neurological function consistent with PRES (headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances).
- *Hypertension*: Advise patients to monitor blood pressure early in the course of therapy and frequently thereafter and report increases of blood pressure or symptoms, such as blurred vision, confusion, severe headache, or nausea and vomiting.
- *Gastrointestinal Perforation and Fistula*: Advise patients to report signs and symptoms of a GI perforation or fistula.
- *Risk of Impaired Wound Healing*: Advise patients that Pazopanib may impair wound healing. Advise patients to inform their healthcare provider of any scheduled surgical procedure.
- *Hypothyroidism and Proteinuria*: Inform patients that thyroid function testing and urinalysis will be performed during treatment.
- *Tumor Lysis Syndrome*: Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS, such as abnormal heart rhythm, seizure, confusion, muscle cramps or spasms, or a decrease in urine output.
- *Infection*: Advise patients to promptly report any signs or symptoms of infection.
- *Embryo-Fetal Toxicity*: Advise female patients to inform their healthcare provider of a known or suspected pregnancy during treatment with Pazopanib. Inform female patients of the risk to a fetus and the potential loss of the pregnancy.
  Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of Pazopanib. Advise male patients with female partners of reproductive potential to use condoms during treatment with Pazopanib and for at least 2 weeks after the last dose.
- *Lactation*: Advise women not to breastfeed during treatment with Pazopanib and for 2 weeks after the last dose.
- *Infertility*: Advise males and females of reproductive potential that Pazopanib may impair fertility.
- *Gastrointestinal Adverse Reactions*: Advise patients on how to manage nausea, vomiting, and diarrhea and to notify their healthcare provider if moderate-to-severe vomiting or diarrhea occurs or if there is a decrease in oral intake.
- *Depigmentation*: Advise patients that depigmentation of the hair or skin may occur during treatment with Pazopanib.
- *Drug Interactions*: Advise patients to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- *Dosage and Administration*: Advise patients to take Pazopanib without food (at least 1 hour before or 2 hours after a meal).

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

C030363-00

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

M.L.No.: 5/MN/TS/2014/F/G

11. DATE OF REVISION

Nov 2021