oncogen

Pazorene (Pazopanib)

پیزورین (پیزوپینب)

WARNING: HEPATOTOXICITY Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See full prescribing information for complete boxed warning.(4.4)

1. NAME OF THE MEDICINAL PRODUCT
Pazorene 200mg Film Coated Tablets
Pazorene 400mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Pazorene 200mg Film Coated Tablets: Each tablet contains Pazopanib HCl equivalent to Pazopanib 200mg.
Pazorene 400mg Film Coated Tablets: Each tablet contains Pazopanib HCl equivalent to Pazopanib 400mg.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Pazorene 200mg Film Coated Tablets: Grey, modified capsule-shaped, film-coated tablets, debossed with "P 200" on one side and plain on the other side.
Pazorene 400mg Film Coated Tablets: White, modified capsule-shaped, film-coated tablets, debossed with "P 400" on one side and plain on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Renal cell carcinoma (RCC)
Pazopanib is indicated for the treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC).
Soft tissue sarcoma (STS)
Pazopanib is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.
Limitation of Use : The efficacy of Pazopanib for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors has not been demonstrated.

4.2 Posology and Method of Administration
Dosage regimen
General target population
The recommended dose of Pazopanib is 800 mg orally once daily.
Dose modifications
Dose modification, either an increase or decrease in dose, should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The daily dose of Pazopanib should not exceed 800 mg.
Special populations
Renal impairment
Renal impairment is not expected to influence Pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥30 mL/min. There is no experience of pazopanib in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis; therefore, use of Pazopanib is not recommended in these patients.
Hepatic impairment
The safety and pharmacokinetics of Pazopanib in patients with pre-existing hepatic impairment have not been fully established. No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin. The dose of Pazopanib should be reduced to 200 mg per day in patients with moderate hepatic impairment. There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 times the upper limit of normal [X ULN] regardless of the ALT value); therefore, use of Pazopanib is not recommended in these patients.
Pediatric patients (below 18 years)
Pazopanib is not recommended for use in children and adolescents under 18 years.
Geriatric patients (above 65 years)
No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.
Method of administration
Pazopanib should be taken without food (at least one hour before or two hours after a meal). Pazopanib should be taken whole with water and must not be broken or crushed. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.
4.3 Contraindications
Pazopanib is contraindicated in patients with hypersensitivity to any of the ingredients.
4.4 Special Warnings and Precautions for Use
Hepatic effects
Cases of hepatic failure (including fatalities) have been reported during use of Pazopanib. In a study with Pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years of age may be at greater risk for ALT >3 X ULN. Patients who carry the *HLA-B**57:01 allele also have an increased risk of Pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving Pazopanib, regardless of genotype or age. The vast majority (over 90%) of all transaminase elevations of any grade occurred in the first 18 weeks. 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 4.
Concomitant use of Pazopanib and simvastatin increases the risk of ALT elevations. Beyond recommending that patients with mild hepatic impairment are treated with 800 mg Pazopanib once daily and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with pre-existing hepatic impairment.
Hypertension
In a study with Pazopanib, events of hypertension including 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, and treated promptly with a combination of standard anti-hypertensive therapy and Pazopanib dose reduction or interruption as clinically warranted. 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.
Posterior reversible encephalopathy syndrome (PRES) and maybe fatal/Reversible posterior leukoencephalopathy syndrome (RPLS)
PRES/RPLS has been reported in association with Pazopanib. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. Pazopanib should be permanently discontinued in patients developing PRES/RPLS.
Interstitial lung disease (ILD)/Pneumonitis
ILD, which can be fatal, has been reported in association with Pazopanib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and Pazopanib should be discontinued in patients developing ILD or pneumonitis.
Cardiac dysfunction
In a study with Pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. 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 judgment). Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.
QT prolongation and torsade de pointes
In a study with Pazopanib, events of QT prolongation or 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 medications that may potentially prolong QT interval, or in patients with relevant pre-existing cardiac disease. When using , baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.
Arterial thromboembolic events
In a study with Pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed.
Fatal events have been observed. Pazopanib should be used with caution in patients who are at increased risk of thromboembolic events or who have had a history of thromboembolic events.
Venous thromboembolic events
In a study with Pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. The incidence was higher in the STS population than in the RCC population.Monitor for signs and symptoms of VTE and PE. Withhold pazopinib and then resume at same dose or permanently discontinue based on severity of VTE
Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA) has been reported in a study of Pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Pazopanib should be permanently discontinued in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.
Hemorrhagic events
In a study with Pazopanib, hemorrhagic events have been reported. Fatal hemorrhagic events have occurred. Pazopanib has not been studied in patients who had 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
Aneurysms and artery dissections
Artery dissections and aneurysms have been reported in association with VEGF pathway inhibitors, including Pazopanib. The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysm and/or artery dissections. Before initiating Pazopanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
Gastrointestinal perforations and fistula
In a study with Pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred. Permanently discontinue Pazopanib in case of gastrointestinal perforation or Grade 4 gastrointestinal fistula. Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.
Wound healing
No formal studies of the effect of Pazopanib on wound healing have been conducted. Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with Pazopanib should be stopped at least 7 days prior to scheduled surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.
Hypothyroidism
In a study with Pazopanib, events of hypothyroidism have occurred. Proactive monitoring of thyroid function tests is recommended at baseline, during treatment, and as clinically indicated and manage hypothyroidism as appropriate.
Proteinuria
In a study with Pazopanib, proteinuria has been reported. Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.
Tumor lysis syndrome (TLS)
Cases of TLS, including fatal cases, have been reported in RCC and STS patients treated with Pazopanib. Patients generally at risk of TLS are those with rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Preventative measures such as treatment of high uric acid levels and intravenous hydration should be considered prior to initiation of Pazopanib. Patients at risk should be closely monitored and treated as clinically indicated.
Infections
Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of pazopinib for serious infections.
Combination with other systemic anti-cancer therapies
Pazopanib is not indicated for use in combination with other anti-cancer agents.
Toxicity in Developing Organs
The safety and effectiveness of pazopinib in pediatric patients have not been established. Pazopanib is not indicated for use in pediatric patients.
Pregnancy
Studies in animals have shown reproductive toxicity. Based on animal reproduction studies and its mechanism of action, Pazopanib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with Pazopanib and for at least 2 weeks following the final dose.
4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Drugs that inhibit or induce cytochrome P450 3A4 enzymes
In 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 CYP3A4 may alter the metabolism of Pazopanib.
CYP3A4, P-gp, BCRP inhibitors
Pazopanib is a substrate for CYP3A4, P-gp and BCRP. Co-administration of Pazopanib with other strong inhibitors of the CYP3A4 family (e.g., itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase Pazopanib concentrations. Grapefruit juice may also increase plasma concentrations of Pazopanib. Co-administration of Pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma Pazopanib concentrations. Concomitant use of Pazopanib with a strong CYP3A4 inhibitor should be avoided. If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of Pazopanib should be reduced to 400 mg daily during concomitant administration. Further dose reduction may be considered if possible drug-related adverse events are observed. Combination with strong P-gp or BCRP inhibitors should be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit P-gp or BCRP is recommended.
CYP3A4 inducers
CYP3A4 inducers such as Rifampicin may decrease plasma Pazopanib concentrations. Pazopanib is not recommended if chronic use of strong CYP3A4 inducers cannot be avoided.
Effects of Pazopinib on CYP substrates
Studies with human liver microsomes showed that Pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an in vitro human PXR assay.The concomitant use of pazopinb with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively.
Effects of Pazopinib on other enzymes and transporters
In studies also showed that Pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 microM, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 and OATP1B1.
Effect of concomitant use of Votrinis and simvastatin
Concomitant use of Pazopanib and simvastatin increases the incidence of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for Pazopanib posology and discontinue simvastatin
Drug-food/drink interactions
Administration of Pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, Pazopanib should be administered at least 1 hour before or 2 hours after a meal.
Medicines that raise gastric pH
Concomitant administration of Pazopanib with esomeprazole decreases the bioavailability of Pazopanib by approximately 40% (AUC and C_{max}), and co-administration of Pazopanib with medicines that increase gastric pH should be avoided. 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
4.6 Fertility, pregnancy and lactation
Pregnancy
There are no adequate data from the use of Pazopanib in pregnant women. Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with Pazopanib. 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. Pregnant women or females of reproductive potential should be advised of the potential risk to a fetus.
Lactation
There is no information regarding the presence of Pazopanib or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Pazopanib, a lactating woman should be advised not to breastfeed during treatment with Pazopanib and for 2 weeks after the final dose.
Fertility
Contraception
Females
Females of reproductive potential should be advised to use effective contraception during treatment with Pazopanib and for at least 2 weeks after the last dose.
Males
Male patients (including those who have had vasectomies) with female partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms while taking Pazopanib and for at least 2 weeks after the last dose.
Infertility
Based on findings from animal studies, Pazopanib may impair fertility in males and females of reproductive potential while receiving treatment.
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 judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.
4.8 Undesirable Effects
Summary of the safety profile
The most important serious adverse reactions identified in the RCC or STS studies were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation, Torsade de Pointes and pulmonary, gastrointestinal and cerebral haemorrhage. Other important serious adverse reactions identified in STS studies included venous thromboembolic events, left ventricular dysfunction and pneumothorax.
Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischaemic stroke.
The most common adverse reactions in RCC and STS studies included: diarrhoea, hair colour change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.
Adverse drug reactions, all grades, which were reported in RCC and STS studies 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 utilised for the classification of frequency: very common; common; uncommon; rare; very rare; and not known.
Tabulated list of adverse reactions
Table 1: Treatment-related adverse reactions reported in RCC studies or during post-marketing period

System Organ Class	Frequency	Adverse reactions
Infections and Infestations	Common	Infections (with or without neutropenia)†
	Uncommon	Gingival infection
		Infectious peritonitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Tumour pain
Blood and lymphatic system disorders	Common	Thrombocytopenia
		Neutropenia
		Leukopenia
	Uncommon	Polycythaemia
	Rare	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†
Endocrine disorders	Common	Hypothyroidism
Metabolism and nutrition disorders	Very common	Decreased appetite[a]
	Common	Hypophosphataemia Dehydration
	Uncommon	Hypomagnesaemia
	Not known	Tumour lysis syndrome*
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Dysgeusia[c]
		Headache
	Common	Dizziness
		Lethargy
		Paraesthesia
		Peripheral sensory neuropathy
	Uncommon	Hypoaesthesia
		Transient ischaemic attack
		Somnolence
		Cerebrovascular accident
		Ischaemic stroke
	Rare	Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome†
Eye disorders	Common	Vision blurred
	Uncommon	Retinal detachment†
		Retinal tear†
		Eyelash discolouration
Cardiac disorders	Uncommon	Bradycardia
		Myocardial infarction
		Cardiac dysfunction[f]
		Myocardial ischaemia
Vascular disorders	Very common	Hypertension
	Common	Hot flush
		Venous thromboembolic event[g]
		Flushing
	Uncommon	Hypertensive crisis
		Haemorrhage
	Rare	Aneurysms and artery dissections†
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis
		Dysphonia
		Dyspnoea
		Haemoptysis
	Uncommon	Rhinorrhoea
		Pulmonary haemorrhage
		Pneumothorax
	Rare	Interstitial lung disease/pneumonitis†
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Abdominal pain[a]
	Common	Stomatitis
		Dyspepsia
		Flatulence
		Abdominal distension
		Mouth ulceration
		Dry mouth
	Uncommon	Pancreatitis
		Rectal haemorrhage
		Haematochezia
		Gastrointestinal haemorrhage
		Melaena
		Frequent bowel movements

		Anal haemorrhage
		Large intestine perforation
		Mouth haemorrhage
		Upper gastrointestinal haemorrhage
		Enterocutaneous fistula
		Haematemesis
		Haemorrhoidal haemorrhage
		Ileal perforation
		Oesophageal haemorrhage
		Retroperitoneal haemorrhage
Hepatobiliary disorders	Common	Hyperbilirubinaemia
		Hepatic function abnormal
		Hepatotoxicity
	Uncommon	Jaundice
		Drug induced liver injury
		Hepatic failure†
Skin and subcutaneous disorders	Very common	Hair colour change
		Palmar-plantar erythrodysaesthesia syndrome
		Alopecia
		Rash
	Common	Skin hypopigmentation
		Dry skin
		Pruritus
		Erythema
		Skin depigmentation
		Hyperhidrosis
	Uncommon	Nail disorders
		Skin exfoliation
		Photosensitivity reaction
		Rash erythematous
		Skin disorder
		Rash macular
		Rash pruritic
		Rash vesicular
		Pruritus generalised
		Rash generalised
		Rash papular
		Plantar erythema
		Skin ulcer†
Musculoskeletal and connective tissue disorders	Common	Arthralgia
		Myalgia
		Muscle spasms
	Uncommon	Musculoskeletal pain
Renal and urinary disorders	Very Common	Proteinuria
	Uncommon	Haemorrhage urinary tract
Reproductive system and breast disorders	Uncommon	Menorrhagia
		Vaginal haemorrhage
		Metrorrhagia
General disorders and administration site conditions	Very common	Fatigue
	Common	Mucosal inflammation
		Asthenia
		Oedema[b]
		Chest pain
	Uncommon	Chills
		Mucous membrane disorder
Investigations	Very common	Alanine aminotransferase increased
		Aspartate aminotransferase increased
	Common	Weight decreased
		Blood bilirubin increased
		Blood creatinine increased
		Lipase increased
		White blood cell count decreased[a]
		Blood thyroid stimulating hormone increased
		Amylase increased
		Gamma-glutamyltransferase increased
		Blood pressure increased
		Blood urea increased
		Liver function test abnormal
	Uncommon	Hepatic enzyme increased
		Blood glucose decreased
		Electrocardiogram QT prolonged
		Transaminase increased
		Thyroid function test abnormal
		Blood pressure diastolic increased
		Blood pressure systolic increased

† 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.

Table 2 Treatment-related adverse reactions reported in STS studies or during post-marketing period

System Organ Class	Frequency	Adverse reactions
Infections and Infestations	Common	Gingival infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very Common	Tumour pain
Blood and lymphatic system disorders[f]	Very Common	Leukopenia
		Thrombocytopenia
		Neutropenia
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)
Endocrine disorders	Common	Hypothyroidism
Metabolism and nutrition disorders	Very common	Decreased appetite
		Hypophosphataemia[f]
	Common	Dehydration
	Uncommon	Hypomagnesaemia
	Not known	Tumour lysis syndrome*
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Very common	Dysgeusia[c]
		Headache
	Common	Peripheral sensory neuropathy
		Dizziness
	Uncommon	Somnolence
		Paresthesia
		Cerebral infarction
Eye disorders	Common	Vision blurred
Cardiac disorders		Cardiac dysfunction[g]
		Left ventricular dysfunction
		Bradycardia
	Uncommon	Myocardial infarction
Vascular disorders	Very common	Hypertension
	Common	Venous thromboembolic event[d]
		Hot Flush
		Flushing
	Uncommon	Haemorrhage
	Rare	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis
		Dysphonia
		Dyspnoea
		Cough
		Pneumothorax
		Hiccups
		Pulmonary haemorrhage
	Unommon	Oropharyngeal pain
		Bronchial haemorrhage
		Rhinorrhoea
		Haemoptysis
	Rare	Interstitial lung disease/pneumonitis†
Gastrointestinal disorders	Very common	Diarrhoea
		Nausea
		Vomiting
		Abdominal pain[a]
		Stomatitis
	Common	Abdominal distension
		Dry mouth
		Dyspepsia
		Mouth haemorrhage
		Flatulence
		Anal haemorrhage
	Uncommon	Gastrointestinal haemorrhage
		Rectal haemorrhage
		Enterocutaneous fistula
		Gastric haemorrhage
		Melaena
		Oesophageal haemorrhage
		Peritonitis
		Retroperitoneal haemorrhage
		Upper gastrointestinal haemorrhage
		Ileal perforation
Hepatobiliary disorders	Uncommon	Hepatic function abnormal
	Not known	Hepatic failure*
Skin and subcutaneous disorders	Very common	Hair colour change
		Skin hypopigmentation
		Exfoliative rash
	Common	Alopecia
		Skin disorder[c]
		Dry skin
		Hyperhydrosis
		Nail disorder
		Pruritus
		Erythema
	Uncommon	Skin ulcer
		Rash
		Rash papular
		Photosensitivity reaction
		Palmar-plantar erythrodysaesthesia syndrome
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain
		Myalgia
		Muscle spasms
	Uncommon	Arthralgia
Renal and urinary disorders	Uncommon	Proteinuria
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage
		Menorrhagia
General disorders and administration site conditions	Very common	Fatigue
	Common	Oedema[b]
		Chest pain
		Chills
	Uncommon	Mucosal inflammation[e]
		Asthenia
Investigations[h]	Very common	Weight decreased
	Common	Ear, nose and throat examination abnormal[h]
		Alanine aminotransferase increased
		Blood cholesterol abnormal
		Aspartate aminotransferase increased
		Gamma glutamyltransferase increased
	Uncommon	Blood bilirubin increased
		Aspartate aminotransferase
		Alanine aminotransferase
		Platelet count decreased
		Electrocardiogram QT prolonged

Paediatric population
The safety and effectiveness of Pazopinib in pediatric patients have not been established.

4.9 Overdose
Pazopanib doses up to 2,000 mg daily have been evaluated in studies. Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg and 1,000 mg daily, respectively. 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.

Symptoms and signs
There is currently limited experience with overdosage in Pazopanib.

Treatment
Further management should be as clinically indicated or as recommended by the national poisons center, where available. 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 Pharmacodynamic Properties

Pharmacotherapeutic group, ATC
Pharmacotherapeutic group: Antineoplastic agents – Protein kinase inhibitor, ATC Code: L01XE11.

Mechanism of action (MOA)
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)-alpha and –beta, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose- dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR- beta receptors in cells. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumor xenografts in mice.

5.2 Pharmacokinetic Properties

Absorption
Pazopanib is absorbed orally with median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and C_{max} when the pazopanib dose increased above 800 mg once daily. Systemic exposure to Pazopanib is increased when administered with food. Therefore, Pazopanib should be administered at least 1 hour before or 2 hours after a meal.T he bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets should not be crushed.

Distribution
Binding of Pazopanib to human plasma protein in vivo was greater than 99% with no concentration dependence over the range of 10 to 100 microgram/mL. In studies suggest that Pazopanib is a substrate for P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP).

Biotransformation/metabolism
Results from studies demonstrated that the metabolism of Pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

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

Special populations

Renal impairment
Renal impairment is not expected to influence Pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥30 mL/min.

Hepatic impairment
The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment was 200 mg once daily. The median steady-state values of after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45% and 39%, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function. There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 X ULN regardless of the ALT value); therefore, use of Pazopanib is not recommended in these patients.

Pharmacogenomics
In a pharmacogenetic meta-analysis of data from 31 clinical studies of Pazopanib administered either as monotherapy or in combination with other agents, ALT > 5 X ULN (NCI CTC Grade 3) occurred in 19% of HLA-B*57:01 allele carriers and in 10% of non-carriers. In this dataset, 133/2235 (6%) of the patients carried the HLA-B*57:01 allele.

6 PHARMACEUTICAL PARTICULARS

6.1 Pack Size
For 200mg & 400mg tablets:
3x 10's (30) tablets.
Alu/Alu blisters having 10 tablets in each blister and packed in unit carton with leaflet.

6.2 Storage Conditions
Do not store above 30°C, Protect from sunlight and moisture.

6.3 Dosage and Instructions
As directed by physician.
Keep out of reach of children.

For adverse event reporting, kindly email us at
pharmacovigilance@oncogenpharma.com.pk

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

7. MANUFACTURER

Manufactured by:
oncogen
Oncogen Pharma (Pvt.) Limited.
Plot No: WH-26 & 27-A3, Korangi Creek
Industrial Park (KCIP), Karachi 75190, Pakistan.
www.oncogenpharma.com.pk