

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

Pregnancy.
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 or its metabolites are excreted in human milk. 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 with pazopanib.

Fertility

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

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 perform tasks that require judgement, motor, or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired, or weak.

Adverse reactions

Summary of Safety Profile

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:

- Very common ≥1/10
- 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)

Categories have been assigned based on absolute frequencies in the clinical trial data. Post-marketing data on safety and tolerability across all pazopanib clinical studies and from spontaneous reports have also been evaluated. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 1: Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period

System Organ Class Frequency	Frequency (all grades)	Adverse reactions (with or without infections)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and Infestations	Uncommon	neutropenia) †	not known	not known	not known
	Uncommon	Gingival infection	1 (<1%)	0	0
	Uncommon	Infectious peritonitis	1 (<1%)	0	0
	Common	Tumor pain	1 (<1%)	1 (<1%)	0
Neoplasms benign, malignant and inspecified (incl cysts and polyps)	Common				
	Common				
	Common				
	Common				
Blood and lymphatic system disorders	Common	Thrombocytopenia	80 (7%)	10 (<1%)	5 (<1%)
	Common	Neutropenia	79 (7%)	20 (2%)	4 (<1%)
	Common	Leucopenia	63 (5%)	5 (<1%)	0
	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
Endocrine disorders	Common	Hypothyroidism	83 (7%)	1 (<1%)	0
	Common	Decreased appetite ^a	317 (28%)	14 (1%)	0
	Common	Hypophosphatemia	21 (2%)	7 (<1%)	0
	Common	Dehydration	16 (1%)	5 (<1%)	0
Metabolism and nutrition disorders	Common	Hypomagnesemia	10 (<1%)	0	0
	Common	Insomnia	30 (3%)	0	0
	Common	Dysgeusia c	254 (22%)	1 (<1%)	0
	Common	Headache	122 (11%)	11 (<1%)	0
Psychiatric disorders	Common	Dizziness	55 (5%)	3 (<1%)	1 (<1%)
	Common	Lethargy	30 (3%)	3 (<1%)	0
	Common	Paresthesia	20 (2%)	2 (<1%)	0
	Common	Peripheral sensory neuropathy	17 (1%)	0	0
Nervous system disorders	Common	Hypoesthesia	8 (<1%)	0	0
	Common	Transient ischemic attack	7 (<1%)	4 (<1%)	0
	Common	Somnolence	3 (<1%)	1 (<1%)	0
	Common	Cerebrovascular accident	2 (<1%)	1 (<1%)	0
Eyes disorders	Common	Ischemic stroke	2 (<1%)	0	1 (<1%)
	Common	Vision Blurred	19 (<2%)	1 (<1%)	0
	Common	Eyelash discoloration	1 (<1%)	1 (<1%)	0
	Common	Bradycardia	6 (<1%)	0	0
Cardiac disorders	Common	Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)
	Common	Cardiac dysfunction ^f	4 (<1%)	1 (<1%)	0
	Common	Myocardial ischemia	3 (<1%)	1 (<1%)	0
	Common	Hypertension	473 (41%)	115 (10%)	1 (<1%)
Vascular disorders	Common	Hot flush	16 (1%)	0	0
	Common	Venous thromboembolic event ^g	13 (1%)	6 (<1%)	7 (<1%)
	Common	Flushing	12 (1%)	0	0
	Common	Hypertensive crisis	6 (<1%)	0	2 (<1%)
Respiratory, thoracic and mediastinal disorders	Common	Hemorrhage	1 (<1%)	0	0
	Common	Epistaxis	50 (4%)	1 (<1%)	0
	Common	Dysphonia	48 (4%)	0	0
	Common	Dyspnoea	42 (4%)	8 (<1%)	1 (<1%)
Gastrointestinal disorders	Common	Hemoptysis	15 (1%)	1 (<1%)	0
	Common	Rhinorrhea	8 (<1%)	0	0
	Common	Pulmonary Hemorrhage	2 (<1%)	0	0
	Common	Pneumothorax	1 (<1%)	0	0
Hepatobiliary disorders	Common	Diarrhea	614 (53%)	65 (6%)	2 (<1%)
	Common	Nausea	386 (34%)	14 (1%)	0
	Common	Vomiting	225 (20%)	18 (2%)	1 (<1%)
	Common	Abdominal pain ^a	139 (12%)	15 (1%)	0
Skin and subcutaneous disorders	Common	Stomatitis	96 (8%)	4 (<1%)	0
	Common	Dyspepsia	83 (7%)	2 (<1%)	0
	Common	Flatulence	43 (4%)	0	0
	Common	Abdominal distension	36 (3%)	2 (<1%)	0
Renal and urinary disorders	Common	Mouth ulceration	28 (2%)	3 (<1%)	0
	Common	Dry mouth	27 (2%)	0	0
	Common	Pancreatitis	8 (<1%)	4 (<1%)	0
	Common	Rectal hemorrhage	8 (<1%)	2 (<1%)	0
Reproductive system and breast disorders	Common	Hematochezia	6 (<1%)	0	0
	Common	Gastrointestinal hemorrhage	4 (<1%)	2 (<1%)	0
	Common	Melena	4 (<1%)	1 (<1%)	0
	Common	Frequent bowel movements	3 (<1%)	0	0
General disorders and administration site conditions	Common	Anal hemorrhage	2 (<1%)	0	0
	Common	Large intestine perforation	2 (<1%)	1 (<1%)	0
	Common	Mouth hemorrhage	2 (<1%)	0	0
	Common	Upper gastrointestinal hemorrhage	2 (<1%)	1 (<1%)	0
Investigations	Common	Enterocutaneous fistula	1 (<1%)	0	0
	Common	Hematemesis	1 (<1%)	0	0
	Common	Hemorrhoidal hemorrhage	1 (<1%)	0	0
	Common	Ileal perforation	1 (<1%)	0	1 (<1%)
Skin and subcutaneous disorders	Common	Esophageal hemorrhage	1 (<1%)	0	0
	Common	Retropertitoneal hemorrhage	1 (<1%)	0	0
	Common	Hyperbilirubinaemia	38 (3%)	2 (<1%)	1 (<1%)
	Common	Abnormal liver function	29 (2%)	13 (1%)	2 (<1%)
Hepatobiliary disorders	Common	Hepatotoxicity	18 (2%)	11 (<1%)	2 (<1%)
	Common	Jaundice	3 (<1%)	1 (<1%)	0
	Common	Drug induced liver injury	2 (<1%)	2 (<1%)	0
	Common	Liver failure	1 (<1%)	0	1 (<1%)
Skin and subcutaneous disorders	Common	Hair color change	404 (35%)	1 (<1%)	0
	Common	Palmar-plantar erythrodysesthesia syndrome	206 (18%)	39 (3%)	0
	Common	Alopecia	130 (11%)	0	0
	Common	Rash	129 (11%)	7 (<1%)	0
Skin and subcutaneous disorders	Common	Skin hypopigmentation	52 (5%)	0	0
	Common	Dry skin	50 (4%)	0	0
	Common	Pruritus	29 (3%)	0	0
	Common	Erythema	25 (2%)	0	0
Skin and subcutaneous disorders	Common	Skin depigmentation	20 (2%)	0	0
	Common	Hyperhidrosis	17 (1%)	0	0
	Common	Nail disorders	11 (<1%)	0	0
	Common	Skin exfoliation	10 (<1%)	0	0
Skin and subcutaneous disorders	Common	Photosensitivity reaction	7 (<1%)	0	0
	Common	Rash erythematous	6 (<1%)	0	0
	Common	Skin disorder	5 (<1%)	0	0
	Common	Rash macular	4 (<1%)	0	0
Skin and subcutaneous disorders	Common	Rash pruritic	3 (<1%)	0	0
	Common	Rash vesicular	3 (<1%)	0	0
	Common	Generalized pruritus	2 (<1%)	1 (<1%)	0
	Common	Generalized rash	2 (<1%)	0	0
Skin and subcutaneous disorders	Common	Papular rash	2 (<1%)	0	0
	Common	Plantar erythema	1 (<1%)	0	0
	Common	Arthralgia	48 (4%)	8 (<1%)	0
	Common	Myalgia	35 (3%)	2 (<1%)	0
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	25 (2%)	0	0
	Common	Musculoskeletal pain	9 (<1%)	1 (<1%)	0
Renal and urinary disorders	Common	Proteinuria	135 (12%)	32 (3%)	0
	Common	Urinary tract hemorrhage	1 (<1%)	0	0
Reproductive system and breast disorders	Common	Menorrhagia	3 (<1%)	0	0
	Common	Vaginal hemorrhage	3 (<1%)	0	0
	Common	Metrorrhagia	1 (<1%)	0	0
	Common	Fatigue	415 (36%)	65 (6%)	1 (<1%)
General disorders and administration site conditions	Common	Mucosal inflammation	86 (7%)	5 (<1%)	0
	Common	Asthenia	82 (7%)	20 (2%)	1 (<1%)
	Common	Edema ^b	72 (6%)	1 (<1%)	0
	Common	Chest pain	18 (2%)	2 (<1%)	0
Investigations	Common	Chills	4 (<1%)	0	0
	Common	Mucous membrane disorder	1 (<1%)	0	0
	Common	Alanine aminotransferase increased	246 (21%)	84 (7%)	14 (1%)
	Common	Incremento de aspartato aminotransferasa	211 (18%)	51 (4%)	10 (<1%)
Investigations	Common	Weight loss	96 (8%)	7 (<1%)	0
	Common	Blood bilirubin increase	61 (5%)	6 (<1%)	1 (<1%)
	Common	Blood creatinine increase	55 (5%)	3 (<1%)	0
	Common	Lipase increase	51 (4%)	21 (2%)	7 (<1%)
Investigations	Common	White blood cell count decrease ^d	51 (4%)	3 (<1%)	0
	Common	Blood thyroid stimulating hormoneincrease	36 (3%)	0	0
	Common	Amylase increase	35 (3%)	7 (<1%)	0
	Common	Gamma-glutamyltransf erase increase	31 (3%)	9 (<1%)	4 (<1%)
Investigations	Common	Blood pressure increase	15 (1%)	2 (<1%)	0
	Common	Blood urea increase	12 (1%)	1 (<1%)	0
	Common	Abnormal liver function test	12 (1%)	6 (<1%)	1 (<1%)
	Common	Liver enzyme increase	11 (<1%)	4 (<1%)	3 (<1%)
Investigations	Common	Blood glucose decrease	7 (<1%)	0	1 (<1%)
	Common	Prolonged electrocardiogram QT	7 (<1%)	2 (<1%)	0
	Common	Transaminase increase	7 (<1%)	1 (<1%)	0
	Common	Abnormal thyroid function test	3 (<1%)	0	0
Investigations	Common	Blood pressure diastolic increase	2 (<1%)	0	0
	Common	Blood pressure systolic increase	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).

The following terms have been combined:

a Abdominal pain, upper abdominal pain and lower abdominal pain

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

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 erythrodysesthesia syndrome were observed more frequently in patients of East Asian descent.

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

System Organ Class Frequency	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	Tumor pain	121 (32%)	32 (8%)	0	
Blood and lymphatic system disorders	Common	Leukopenia	106 (44%)	3 (1%)	0	
	Common	Thrombocytopenia	86 (36%)	7 (3%)	2 (<1%)	
	Common	Neutropenia	79 (33%)	10 (4%)	0	
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uraemic syndrome)	1 (<1%)	1 (<1%)	0	
Endocrine disorders	Common	Hypothyroidism	18 (5%)	0	0	
Metabolism and nutrition disorders	Very common	Appetite decrease ^a	108 (28%)	12 (3%)	0	
	Very common	Hypoalbuminemia ^a	81 (34%)	2 (<1%)	0	
	Common	Dehydration	4 (1%)	2 (1%)	0	
	Uncommon	Hypomagnesaemia	1 (<1%)	0	0	
Psychiatric disorders	Common	Insomnia	5 (1%)	1 (<1%)	0	
Nervous system disorders	Very common	Dysgeusia ^a	79 (21%)	0	0	
	Very common	Headache	54 (14%)	2 (<1%)	0	
	Common	Peripheral sensory neuropathy	30 (8%)	1 (<1%)	0	
	Common	Dizziness	15 (4%)	0	0	
	Uncommon	Somnolence	3 (<1%)	0	0	
	Uncommon	Paresthesia	1 (<1%)	0	0	
	Uncommon	Cerebral infarction	1 (<1%)	0	1 (<1%)	
Eyes disorders	Uncommon	Blurred vision	15 (4%)	0	0	
Cardiac disorders	Common	Cardiac dysfunction ^g	21 (5%)	3 (<1%)	1 (<1%)	
	Common	Left ventricular dysfunction	13 (3%)	3 (<1%)	0	
	Common	Bradycardia	4 (1%)	0	0	
Vascular disorders	Uncommon	Myocardial infarction	1 (<1%)	0	0	
	Very common	Hypertension	152 (40%)	26 (7%)	0	
	Common	Venous thromboembolic event ^d	13 (3%)	4 (1%)	5 (1%)	
Respiratory, thoracic and mediastinal disorders	Common	Hot flush	12 (3%)	0	0	
	Common	Flushing	4 (1%)	0	0	
	Uncommon	Hemorrhage	2 (<1%)	1 (<1%)	0	
	Common	Epistaxis	22 (6%)	0	0	
	Common	Dysphonia	20 (5%)	0	0	
	Common	Dyspnea	14 (4%)	3 (<1%)	0	
	Common	Cough	12 (3%)	0	0	
	Common	Pneumothorax	7 (2%)	2 (<1%)	1 (<1%)	
	Common	Hiccups	4 (1%)	0	0	
	Common	Pulmonary hemorrhage	4 (1%)	1 (<1%)	0	
	Uncommon	Oropharyngeal pain	3 (<1%)	0	0	
	Uncommon	Bronchial hemorrhage	2 (<1%)	0	0	
	Uncommon	Rhinorrhea	1 (<1%)	0	0	
	Uncommon	Hemoptysis	1 (<1%)	0	0	
	Gastrointestinal disorders	Very common	Diarrhea	174 (46%)	17 (4%)	0
		Very common	Nausea	167 (44%)	7 (2%)	0
Very common		Vomiting	96 (25%)	8 (2%)	0	
Very common		Abdominal pain ^a	55 (14%)	15 (1%)	0	
Very common		Stomatitis	41 (11%)	1 (<1%)	0	
Common		Abdominal distension	16 (4%)	2 (1%)	0	
Common		Dry mouth	14 (4%)	0	0	
Common		Dyspepsia	12 (3%)	0	0	
Common		Mouth hemorrhage	5 (1%)	0	0	
Common		Flatulence	5 (1%)	0	0	
Common		Anal hemorrhage	4 (1%)	0	0	
Uncommon		Gastrointestinal hemorrhage	2 (<1%)	0	0	
Uncommon		Rectal hemorrhage	2 (<1%)	0	0	
Uncommon		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0	
Uncommon		Gastric hemorrhage	1 (<1%)	0	0	
Uncommon		Malena	2 (<1%)	0	0	
Uncommon		Esophageal hemorrhage	1 (<1%)	0	1 (<1%)	
Uncommon		Peritonitis	1 (<1%)	0	0	
Uncommon		Retropertitoneal hemorrhage	1 (<1%)	1 (<1%)	0	
Uncommon		Upper gastrointestinal hemorrhage	1 (<1%)	1 (<1%)	0	
Uncommon		Ileal perforation	1 (<1%)	0	1 (<1%)	
Hepatobiliary disorders		Uncommon	Abnormal hepatic function	2 (<1%)	0	1 (<1%)
Skin and subcutaneous disorders		Very common	Hair colour change	93 (24%)	0	0
		Very common	Skin hypopigmentation	80 (21%)	0	0
		Very common	Exfoliative rash	52 (14%)	2 (<1%)	0
		Common	Alopecia	30 (8%)	0	0
	Common	Skin disorder ^c	26 (7%)	4 (1%)	0	
	Common	Dry skin	21 (5%)	0	0	
	Common	Hyperhidrosis	18 (5%)	0	0	
	Common	Nail disorder	13 (3%)	0	0	
	Common	Pruritus	11 (3%)	0	0	
	Common	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 erythrodyssaes- thesia syndrome	2 (<1%)	0	0	
	Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain	35 (9%)	2 (<1%)	0
		Common	Myalgia	28 (7%)	2 (<1%)	0
		Common	Muscle spasm	8 (2%)	0	0
		Uncommon	Arthralgia	2 (<1%)	0	0
Renal and urinary disorders	Uncommon	Proteinuria	2 (<1%)	0	0	
Reproductive system and breast disorders	Uncommon	Vaginal hemorrhage	3 (<1%)	0	0	
	Uncommon	Menorrhagia	1 (<1%)	0	0	
General disorders and administration site conditions	Very common	Fatigue	178 (47%)	34 (9%)	1 (<1%)	
	Common	Edema ^b	18 (5%)	1 (<1%)	0	
	Common	Chest pain	12 (3%)	4 (1%)	0	
	Common	Chills	10 (3%)	0	0	
	Uncommon	Mucosal inflammation ^e	1 (<1%)	0	0	
	Uncommon	Asthenia	1 (<1%)	0	0	
Investigations ^h	Very common	Weight loss	86 (23%)	5 (<1%)	0	
	Common	Ear, nose and throat examination abnormal ^a	29 (8%)	4 (1%)	0	
	Common	Alanine aminotransferase increase	8 (2%)	4 (1%)	2 (<1%)	
	Common	Abnormal blood cholesterol	6 (2%)	0	0	
	Common	Aspartate aminotransferase increased	5 (1%)	2 (<1%)	2 (<1%)	
	Common	Gamma-glutamyltransferase increase	4 (1%)	0	3 (<1%)	
	Uncommon	Blood bilirubin increase	2 (<1%)	0	0	
	Uncommon	Aspartate aminotransferase	2 (<1%)	0	2 (<1%)	
	Uncommon	Alanine aminotransferase	1 (<1%)	0	1 (<1%)	
	Uncommon	Platelet count decreased	1 (<1%)	0	1 (<1%)	
Uncommon	Prolonged electrocardiogram QT	2 (<1%)	1 (<1%)	0		