DRUG NAME: Pazopanib

SYNONYM(S): pazopanib hydrochloride, GW786034[1]

COMMON TRADE NAME(S): VOTRIENT®

CLASSIFICATION: vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Pazopanib is an orally active tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR-1,-2, -3), platelet-derived growth factor receptor (PDGFR-α,-β), and stem cell factor receptor (c-KIT).[2] Similar to sunitinib or sorafenib, pazopanib is reported to block tumour growth by interfering with angiogenesis. Pazopanib is also an inhibitor of fibroblast growth factor receptor (FGFR-1 and -3), the interleukin receptor (IL-2), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).[3-5]

PHARMACOKINETICS:

Oral Absorption	14-39%[6]; increased with food or crushed tablet; time to peak plasma concentration 2-4 h; solubility is pH dependent (reduced absorption with increasing pH)[7]	
Distribution	highly protein bound to P-glycoprotein (Pgp) and Breast Cancer Resistant Protein (BCRP)	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	> 99%
Metabolism	primarily by CYP 3A4, minor metabolism by CYP 1A2 and CYP 2C8	
	active metabolite(s)[6]	activity not characterized
	inactive metabolite(s)[6]	activity not characterized
Excretion	primarily in feces	
	urine	< 4%
	feces	60-70% unchanged; 7-15% as metabolites
	terminal half life	31 h
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Renal cell carcinoma

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:
- thrombotic event within the previous 6 months[2]

Caution:

- in patients with ***uncontrolled or significant cardiac disease*** including hypertension, myocardial infarction/ischemia, congestive heart failure, left ventricular ejection fraction less than 45% or QT prolongation[2,8]**;** see paragraph in **Side Effects** section
- ***Hepatotoxicity*** (including hepatic failure and fatalities) has been reported. Liver enzyme tests are recommended at baseline and at routine intervals during treatment. Caution is advised in patients with a baseline bilirubin greater than 1.5 X ULN and/or AST greater than 2 X ULN.[9,10] See paragraph in **Side Effects** section. Concomitant use of simvastatin may increase the risk of ALT elevations.[9,10] See **Interactions** section.
- ***Wound healing complications*** are a risk for VEGF inhibitors. Hold pazopanib for at least 7 days prior to surgery and resume 4 weeks after surgery based on clinical judgment of adequate wound healing.[2]
- Potential ***drug interactions*** involving CYP 3A4, P-glycoprotein, BCRP, UGT1A1 or OATP1B1 may affect the absorption or elimination of pazopanib.[2] See paragraph in **Interactions** section.

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Pazopanib is not clastogenic in *in vitro* chromosome tests.[2]

Fertility: In female animals, pazopanib reduced fertility by loss of implantation, early resorption, decreased corpora lutea and ovarian atrophy. Male fertility was not affected in animal studies.[2]

Pregnancy: FDA Pregnancy Category D.[11] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). In animal studies, pazopanib has been shown to be teratogenic, causing cardiovascular malformations, delayed ossification, reduced fetal body weight, and loss of embryo. It is advisable to avoid becoming pregnant while receiving pazopanib and for up to 8 weeks after ending treatment.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	leucopenia (37%, severe 0%)
	lymphopenia (31%, severe 4%)
	neutropenia (34%, severe 1%)
	thrombocytopenia (32%, severe <1%)
cardiac (see paragraph following **Side Effects** table)	congestive heart failure and decreased LVEF (<1%)
	myocardial infarction/ischemia (<2%)
endocrine	hypothyroidism (3%)[12]
	TSH, elevated (29%, severe 4%)[12]
gastrointestinal	*emetogenic potential: low*[13]
	abdominal pain (11%, severe 2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (52%, severe 3%)[14]; plasma pazopanib concentration-dependent[15]
	dyspepsia (5%)
	nausea (26%, severe <1%)
	pancreatitis (<1%)
	perforation or fistula (<1%, severe <1%)[6,11]
	rectal hemorrhage (1%)
	stomatitis (4%); plasma pazopanib concentration-dependent[15]
	vomiting (21%, severe 2%)
	weight loss (9%)
general disorders and administration site conditions	asthenia (14%, severe 3%)
	chest pain, non-cardiac (5%)
	fatigue (19%, severe 2%)
hepatobiliary	hepatic function, abnormal (3%)
	hepatotoxicity (2%, severe <1%)[2,16]; see paragraph following **Side Effects** table
infections and infestations	urinary tract infection (4%)
investigations	ALT, increased (53%, severe 10-18%)[2,17]; plasma pazopanib concentration-dependent[15]; see paragraph following **Side Effects** table
	AST, increased (53%, severe 7%); see paragraph following **Side Effects** table
	creatinine, increased (26%, severe <1%)
	hyperbilirubinemia (36%, severe 3%); see paragraph following **Side Effects** table
	hypocalcemia (33%, severe 1%)
	hypomagnesemia (26%, severe 1%)
	hyponatremia (31%, severe 4%)
	hypophosphatemia (34%, severe 4%)
	lipase, increased (4%)
	QT prolongation ≥ 500 msec (1%); see paragraph following **Side Effects** table
	serum amylase, increased (3%)
	Torsade de Pointes (<1%); see paragraph following **Side Effects** table
metabolism and nutrition	***anorexia*** (22%, severe 2%)
	hypoglycemia (17%, severe <1%)
	hyperglycemia (41%, severe <1%)
	hyperkalemia (27%, severe 4%)
nervous system	dysgeusia (8%)
	headache (10%, severe 0%)
	paraesthesia (3%)
	transient ischemic attack (<2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
renal and urinary	dysuria (2%)
	hematuria (4%)
	proteinuria (9%, severe <1%)[2,11]
respiratory, thoracic and mediastinal	epistaxis (2%)
	hemoptysis (2%)
skin and subcutaneous tissue	alopecia (8%)
	hair colour changes, depigmentation (38%); plasma pazopanib concentration-dependent[15]
	hyperhidrosis (3%)
	palmar-plantar erythrodysesthesia (6%); plasma pazopanib concentration-dependent[15]
	rash (8%)
	skin depigmentation (3%); following 1 or 2 cycles, dose-dependent[3]
vascular (see paragraph following **Side Effects** table)	***cerebral hemorrhage*** (<1%)
	cerebral vascular accident (<1%)
	hypertension (40%, severe 4%)
	hypertensive crisis (<1%)

Adapted from standard reference[2] unless specified otherwise.

Arterial thrombotic events including myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed. Use with caution in those who are at increased risk of thrombotic events or who have had a history of thrombotic events.[2]

Cardiac dysfunction has been reported with decreases in left ventricular ejection fraction (LVEF).[2] Cardiac assessment for symptomatic congestive heart failure (CHF) or reduced LVEF may be needed.[18] Use caution in patients with LVEF less than 45%.[8]

Hypertension is common and usually occurs within the first 18 weeks of treatment. Persistent hypertension can be managed with antihypertensive agents or dose reductions of pazopanib. Rarely, hypertensive crisis may occur in patients with or without a history of hypertension. In the event of hypertensive crisis or severe and persistent hypertension, discontinue pazopanib.[2]

QT Prolongation (≥ 500 msec) has been reported and may lead to Torsade de Pointes. Caution is advised in patients with a history of QT interval prolongation or taking antiarrhythmics or other medications that may prolong the QT interval. Patients who are at risk for developing Torsade de Pointes, including those with diabetes mellitus, autonomic neuropathy and electrolyte disturbances, should be closely monitored.[2] Baseline and periodic electrocardiograms and electrolytes may be needed.[2,18]

Cases of ***hepatotoxicity***, including fatalities (0.1%) have been reported.[2,16] In clinical trials, increases in serum transaminases and bilirubin were observed. In most cases, however, isolated increases in ALT and AST were reported without concomitant elevations in alkaline phosphatase or bilirubin and the majority of all transaminase elevations (92.5%) of any grade occurred in the first 18 weeks of treatment. Monitor for signs and symptoms of hepatic dysfunction: jaundice, unusual darkening of the urine, anorexia, nausea, fatigue, right upper abdominal discomfort and vomiting.[2] Frequent routine monitoring of liver enzyme tests is recommended for the first few months of treatment and whenever clinically indicated. Dose modification or treatment interruption/cessation may be required.[9,10] Patients with known or suspected Gilbert's syndrome have a defect in the UGT1A gene which when combined with pazopanib's ability to inhibit UGT1A1 results in hyperbilirubinemia. These patients should be

managed as per the recommendations for isolated ALT elevations.[2] Refer to protocol by which patient is being treated.

INTERACTIONS :

AGENT	EFFECT	MECHANISM	MANAGEMENT
esomeprazole[7]	pazopanib bioavailability reduced by ~40% (AUC, Cmax); reduced systemic exposure of pazopanib metabolites	pH-dependent solubility (i.e., reduced pazopanib solubility with increasing pH)	avoid concurrent therapy with proton pump inhibitors, H_2 receptor antagonists, and short acting antacids[7]
grapefruit/grapefruit juice[2,19]	may increase plasma level of pazopanib	may inhibit CYP 3A4 metabolism of pazopanib	avoid grapefruit juice for 48 hours before and on day of dose
ketoconazole[11,19]	may increase plasma level of pazopanib	may inhibit CYP 3A4 metabolism of pazopanib	avoid concurrent therapy if possible; may decrease pazopanib dose by 400 mg
lapatinib[2]	may increase plasma level of pazopanib 50-60%	may inhibit CYP 3A4, Pgp, and BCRP metabolism of pazopanib	avoid concurrent therapy if possible; may decrease pazopanib dose by 200-400 mg
simvastatin[9,20,21]	increased risk of ALT elevations; may increase risk of hepatotoxicity	unknown	monitor liver function • for ALT elevations, modify pazopanib as per protocol and discontinue simvastatin • caution is advised for other statins

Pazopanib is a substrate of CYP 3A4, P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).[2]
Inducers of CYP 3A4 or PgP may increase the metabolism of pazopanib and decrease its systemic effect. Avoid concurrent use.[2]
Inhibitors of CYP 3A4 or PgP may decrease the metabolism of pazopanib and increase its systemic effect.[2] If concurrent administration of a strong CYP 3A4 inhibitor cannot be avoided, consider reducing the dose of pazopanib to 400 mg.[6,11,22]

Pazopanib is a potent inhibitor of UGT1A1 (UDP, A1 family of proteins) and OATP1B1 (1B1 family of proteins) *in vitro*. Use caution with concurrent administration with substrates of these proteins.[2]

Concurrent therapy with drugs that prolong QT interval should be avoided, if possible, due to the risk of potentially fatal arrhythmias.[19,23]

Pazopanib is a weak inhibitor of CYP 3A4, 2D6, 2C8, 1A2, 2C9 and 2C19 *in vivo*. Avoid coadministration of pazopanib with drugs with a narrow therapeutic index that are substrates for CYP 3A4, CYP 2D6 and CYP 2C8. Pazopanib does not have a clinically relevant effect on the substrates of CYP 1A2, CYP 2C9 or CYP 2C19 in cancer patients.[2]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies pazopanib as 200 mg and 400 mg film-coated tablets. Store at room temperature.[24]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count

(ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Oral:	800 mg PO once daily Administer on an empty stomach (one hour before or 2 hours after a meal). Tablet must not be broken or crushed; swallow whole with a glass of water.[2]
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no adjustment required for mild or moderate impairment (creatinine clearance = 30-150 mL/min)[6,11]; not recommended in severe impairment[2]
Dosage in hepatic failure:	not recommended in patients with baseline bilirubin elevations >1.5 x ULN and ALT elevations >2 x ULN or with moderate to severe hepatic impairment[2]
Dosage in dialysis:	no information found

Children: no information found

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