

**Drug Monograph**

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**A - Drug Name**

# pazopanib

**COMMON TRADE NAME(S):** Votrient®

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**B - Mechanism of Action and Pharmacokinetics**

Pazopanib is a multi-target tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR-1, 2 and 3), platelet-derived growth factor (PDGFR- $\alpha$  and  $-\beta$ ), stem cell factor receptor (c-KIT), fibroblast growth factor receptor (FGFR-1 and 3), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte specific protein tyrosine kinase (Lck) and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).

Absorption	Bioavailability reaches saturation at 800mg as it is limited by solubility. Peak concentrations 2-4 hours after oral dose. Up to 4-fold accumulation with daily dosing. Increased exposure when administered as crushed tablets or given with food.	
Distribution	Cross blood brain barrier?	No information found
	PPB	>99%
Metabolism	Pazopanib is metabolized primarily by CYP3A4 (major), CYP1A2 (minor) and CYP2C8 (minor).	
	Active metabolites	Unknown
	Inactive metabolites	yes

Elimination	Half-life	31 hours
	Feces	60-70 % unchanged 7-15 % as metabolites
	Urine	< 4%

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## C - Indications and Status

### Health Canada Approvals:

- Renal cell carcinoma (RCC)
- Soft tissue sarcoma (STS)

Refer to the product monograph for a full list and details of approved indications

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**D - Adverse Effects**

**Emetogenic Potential:** Minimal – No routine prophylaxis; PRN recommended

The side effects and incidences below were reported in the mRCC phase 3 clinical study (where incidence  $\geq$  2% more than placebo). Severe or life-threatening adverse effects are also included from other sources and post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (3%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Bradycardia (12%) (rarely symptomatic)	E
	Ejection fraction decreased (13%) (<1% severe)	D
	Hypertension (40%) (7% severe)	E
	QT interval prolonged (1%) (may be severe)	E
	Venous thromboembolism (5%)	E
Dermatological	Alopecia (8%)	E
	Hair colour changes (38%)	E
	Hand-foot syndrome (6%)	E
	Nail disorder (5%)	E
	Rash (8%)	E
	Skin discolouration (3%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia (22%)	E
	Diarrhea (52%)	E
	Dyspepsia (5%)	E
	Gastrointestinal fistula (1%) (or perforation)	E
	Mucositis (4%)	E
	Nausea, vomiting (26%)	I
General	Fatigue (19%)	E
Hematological	Hemorrhage (13%) (3% severe)	E
	Myelosuppression $\pm$ infection (8%) (may be severe)	E
	Thrombotic microangiopathy (rare)	E
Hepatobiliary	$\uparrow$ LFTs (18%) (may be severe)	E

	↑ Lipase (4%) (including ↑ amylase)	E
	Pancreatitis (<1%)	D
Infection	Infection ± neutropenia (rare; may be severe)	E
Metabolic / Endocrine	Hyperglycemia (<1%) (severe)	E
	Hypoglycemia (<1%) (severe)	E
	Hypothyroidism (7%) (↑ TSH - 34%)	D
	Tumour lysis syndrome (rare; may be fatal)	I E
Musculoskeletal	Musculoskeletal pain (23%)	E
Nervous System	Dizziness (11%)	E
	Dysgeusia (8%)	E
	Headache (10%)	E
	Posterior reversible encephalopathy syndrome (PRES) / PRES (rare)	E
Ophthalmic	Retinal detachment (rare)	E
Renal	Proteinuria (9%) (may be severe)	E
Respiratory	Cough, dyspnea (20%)	E
	Dysphonia (4%)	E
	Pneumonitis (ILD; rare)	E D
	Pneumothorax (3%) (with lung metastases)	E
Urinary	Urinary fistula (urogenital, with previous pelvic radiation, rare)	E

\* "Incidence" may refer to an absolute value or the higher value from a reported range.  
 "Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

\*\* I = *immediate* (onset in hours to days)    E = *early* (days to weeks)  
 D = *delayed* (weeks to months)    L = *late* (months to years)

The most common side effects for pazopanib include diarrhea, hyperglycemia, hypertension, hair colour changes, ↑ lipase/amylase, nausea, vomiting, musculoskeletal pain, anorexia, cough, dyspnea and fatigue.

Approximately 90% of **hypertension** occurs in the first 18 weeks of treatment. Only patients with diastolic BP ≤ 90 mmHg and systolic BP ≤ 140 mmHg were enrolled in the phase III clinical trial. Hypertensive crisis was reported in patients with or without a history of hypertension.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

**RPLS and PRES** (reversible posterior leukoencephalopathy syndrome/posterior reversible encephalopathy syndrome) have occurred within 90 days of starting treatment and may be fatal; a history of new onset hypertension, often severe, was reported in all cases. Pazopanib should be discontinued and RPLS/PRES appropriately investigated and treated.

**Hepatotoxicity** has been reported, usually occurs in the first 18 weeks of treatment and may be severe / fatal in some instances. Patients with HLA-B\*57-01 alleles have a higher rate of severe hepatotoxicity. The incidence may be higher with concomitant statin use.

The most common **hemorrhagic events** were hematuria, epistaxis and hemoptysis, which may be severe / fatal.

**Thrombotic microangiopathy** (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) have been reported post-marketing in combination with bevacizumab.

Cases of non-exudative **retinal detachment** have been reported. Most cases resolved after treatment; pazopanib was continued or resumed; however, recurrence has been reported.

**Interstitial Lung Disease (ILD)/Pneumonitis**, including fatal cases, have been reported. Ground glass opacities were detected by CT scan in some patients, others presented with dyspnea, cough, or fever. Patients should be advised to inform their health care team immediately of any new or worsening respiratory symptoms.

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## E - Dosing

Refer to protocol by which patient is being treated.

**Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the [hepatitis B virus screening and management](#) guideline.

Hypertension must be controlled before starting pazopanib.

Electrolytes should be maintained within the normal range.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

VEGF inhibitors may impair wound healing; pazopanib should be stopped at least 7 days prior to planned surgery.

**Adults:**

Dose: 800mg PO once daily

**Dosage with Toxicity:**

Dose levels: 800mg, 600mg, 400mg, (200mg can be considered if benefit outweighs risk).  
Doses reduced for toxicity should not be re-escalated.

Toxicity / Event	Action
Mild myelosuppression	Hold until ANC $\geq 1.5 \times 10^9/L$ and Platelets $\geq 100 \times 10^9/L$
Persistent hypertension despite anti-hypertensive therapy	Reduce dose; see <a href="#">Management of Angiogenesis Inhibitor (AI)-Induced Hypertension</a> .
Urine protein $\geq 3$ grams/24h	Hold until urine protein $< 3$ grams/24h; restart with $\downarrow 1$ dose level. Discontinue if recurs or develops severe nephrotic syndrome.
Hepatotoxicity	See table below
Serious infections	Consider hold or discontinuing pazopanib
Planned surgery	Hold for at least 7 days pre-surgery
Pneumonitis/ILD	Hold and investigate. If confirmed, discontinue
Retinal detachment	Hold and refer to ophthalmologist for treatment.* Once resolved, consider risk vs. benefit of restarting. Discontinue if recurs.
Wound dehiscence	Discontinue
Nephrotic syndrome, arterial thromboembolism, significant bleeding, grade 4 related organ toxicity, perforation, fistula, RPLS/PRES, thrombotic microangiopathy	
Uncontrollable hypertension or hypertensive crisis	

\*Recommendation for ocular toxicity with VEGF inhibitors (Renouf 2012)

**Hepatic Impairment During Treatment**

Bilirubin during treatment		ALT or AST during treatment	Action
		3 – 8 x ULN (isolated ↑)	Continue treatment; LFTs weekly until ≤ grade 1 or baseline
		> 8 X ULN	Hold until ≤ grade 1. May restart if appropriate, ↓ to 400mg once daily; LFTs weekly x 8. Discontinue permanently if LFTs > 3 x ULN recurs.
>2 x ULN*	AND	> 3 x ULN	Discontinue permanently. Monitor liver function until recovery to grade 1 or baseline.
> ULN (isolated ↑) AND no signs and symptoms of liver injury	AND	< ULN	Caution; no dose adjustment needed. Investigate underlying cause.

\* if mild and related to Gilbert's syndrome may treat as if isolated AST/ALT elevations.

**Dosage with Hepatic Impairment:**

Pazopanib should not be used in patients with baseline bilirubin > 1.5 x ULN and AST or ALT > 2 x ULN, or those who have moderate-severe hepatic impairment. Avoid concomitant statins.

Clearance decreased by 50% in patients with moderate hepatic impairment and dose-limiting toxicity was observed at 400mg.

Use caution in patients with mild hepatic impairment as it has not been formally studied in these patients.

**Dosage with Renal Impairment:**

No dose adjustments are recommended for patients with mild or moderate renal impairment. Not recommended for use in patients with severe renal impairment (< 30 mL/min) as it has not been studied in this patient population.

**Dosage in the elderly:**

No dose adjustment required. Patients over age 60 may be at greater risk of elevated liver enzymes (ALT > 3 x ULN). Although no other differences in response were found between older and younger patients, older patients may be more sensitive to adverse effects.

**Dosage based on ethnicity:**

Myelosuppression and hand-foot syndrome were observed more frequently in East Asian patients.

**Children:**

Not recommended for use in children less than 18 years of age. Contraindicated in patients under 2 years of age. Epiphyseal and dental growth abnormalities, severe effects on body weight gain, organ growth and maturation have been observed in animal studies.

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## F - Administration Guidelines

- Swallow tablet(s) whole with a glass of water.
- Do not cut, crush or chew tablets, as this may increase drug exposure and side effects.
- Take each dose on an empty stomach, at least 1 hour before or 2 hours after a meal. Administration with meals doubles exposure.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- A missed dose may be taken if there are more than 12 hours until the next dose.
- Store between 15-30°C.

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## G - Special Precautions

### Contraindications:

- Patients who are hypersensitive to the drug or its components
- Patients less than 2 years of age

### Other Warnings/Precautions:

- Pazopanib should not be used in patients who have had a thrombotic event within the past 6 months and is not recommended in patients with a history of hemoptysis, cerebral or significant GI bleeding in the past 6 months.
- Use with caution in patients:
  - with risk factors for Torsades de Pointes (history of QT prolongation, antiarrhythmics, medications that prolong the QT interval, cardiac disease, electrolyte disturbances, diabetes or autonomic neuropathy);
  - with bradycardia at baseline, a history of syncope or arrhythmia, ischemic heart disease or congestive heart failure;
  - with an increased risk of or a history of thrombotic events;
  - with a significant risk of hemorrhage;
  - at risk of GI perforation or fistula;
  - with hypothyroidism;
  - on medications that can lead to bradycardia or which are hepatotoxic.
- Pazopanib is not indicated for use in combination with other anticancer agents; increased toxicity and/or mortality has been observed in combination with pemetrexed, lapatinib, or pembrolizumab.

**Other Drug Properties:**

- Carcinogenicity: Probable  
Studies in animals showed increased incidences of liver adenomas and duodenal adenocarcinomas. Relevance to humans is unclear.

**Pregnancy and Lactation:**

- Mutagenicity: No
- Clastogenicity: No
- Fetotoxicity: Documented in animals
- Embryotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Abortifacient effects: Documented in animals
- Pregnancy:  
Pazopanib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for **8 weeks** after the last dose
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **2 weeks** after the last dose.
- Breastfeeding:  
Breastfeeding is not recommended during treatment.
- Fertility effects: Probable  
Documented in animal studies

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**H - Interactions**

Substrate of CYP3A4, P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP). Potent inhibitor of UGT1A1 and OATP1B1; weak inhibitor of CYP3A4, 2D6 and 2C8.

Co-administration with inhibitors that simultaneously target Pgp, BCRP and/or CYP3A4 (e.g. lapatinib) should be avoided due to risk of increased pazopanib exposure (refer to details below).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inducers (i.e. rifampin, St. John's wort)	↓ pazopanib concentrations and effectiveness	↑ pazopanib metabolism	Avoid. Do not use pazopanib in patients who cannot avoid chronic use of strong CYP3A4 inducers; use alternative drug options with no or minimal enzyme induction potential.
Strong CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	Avoid. If must co-administer, ↑ pazopanib concentrations and/or toxicity	↓ metabolism of pazopanib	Avoid. If must co-administer, ↓ pazopanib to 400 mg daily (or lower if toxicity occurs).
CYP3A4 substrates (i.e. midazolam)	↑ substrate concentration and effects/toxicity	Pazopanib can inhibit CYP3A4	Avoid CYP3A4 substrates with narrow therapeutic ranges
UGT1A1 or OATP1B1 substrates (i.e. irinotecan, rosuvastatin)	↑ substrate concentrations and/or toxicity	Pazopanib ↓ substrate elimination by UGT1A1 and OATP1B1	Caution; monitor.
CYP2C8 substrates (i.e. paclitaxel)	↑ substrate concentration and effects/toxicity	Pazopanib inhibits CYP2C8	Avoid CYP2C8 substrates with a narrow therapeutic range
CYP2D6 substrates (i.e. dextromethorphan)	↑ substrate concentration and effects/toxicity	Pazopanib inhibits CYP2D6	Avoid CYP2D6 substrates with a narrow therapeutic range

P-glycoprotein inducers (i.e. rifampin, dexamethasone)	↓ pazopanib concentrations and effectiveness	↑ pazopanib efflux	Avoid concurrent use
Strong P-glycoprotein inhibitors (i.e. grapefruit juice, quinidine, lapatinib, cyclosporine A) or BCRP inhibitors (e.g. cyclosporine, gefitinib, lapatinib)	↑ pazopanib concentration and/or toxicity	↓ pazopanib efflux	Avoid concurrent use
Combined inhibitors of P-glycoprotein, BCRP and/or CYP3A4	↑ substrate concentrations and/or toxicity	↓ pazopanib metabolism or efflux	Avoid
Drugs that ↑ QT interval (i.e. haloperidol, erythromycin, granisetron, amitriptyline, quinidine)	↑ risk of ↑ QT interval	May ↑ QT-prolonging effect	Caution; monitor patient
Drugs that ↑ risk of bleeding (i.e. warfarin, NSAIDs, anticoagulants)	↑ risk of hemorrhagic events	May potentiate effect	Caution; monitor
Drugs that can decrease the heart rate (e.g. antiarrhythmics, beta-blockers, non-dihydropyridine Ca channel blockers, cholinesterase inhibitors, sphingosine-1 phosphate receptor	↓ risk of heart rate	Additive	Caution; monitor patient

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modulators)

Simvastatin	ALT elevations reported	Additive hepatotoxicity	Consider alternatives to pazopanib or discontinuing simvastatin. Close monitoring of patients if statins are used.
Drugs that increase gastric pH (i.e. PPIs, H2-antagonists)	↓ pazopanib absorption and exposure (up to 40%)	pH-dependent absorption	Avoid. Consider antacids and separate dosing by several hours.

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## I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the [hepatitis B virus screening and management](#) guideline for monitoring during and after treatment.

### **Recommended Clinical Monitoring**

Monitor Type	Monitor Frequency
Blood pressure	Baseline (2 readings separated by 24 hours for patients on anti-hypertensives at baseline), then within one week after starting pazopanib, and at each visit
Liver function tests	Baseline, at weeks 2, 4, 6, 8, at months 3 and 4, then as clinically indicated; monitor more frequently in patients with known HLA-B*57:01 allele
CBC	Baseline and at each visit
Renal function tests	Baseline and at each visit
Urinalysis	Baseline and at each visit
ECG	Baseline and as clinically indicated
Electrolytes, including magnesium, calcium, phosphate	Baseline and as clinically indicated
Blood glucose, lipase and amylase	Baseline and as clinically indicated
Thyroid function tests	Baseline and as clinically indicated
LVEF in patients at risk (including those who have received prior anthracyclines)	Baseline and as clinically indicated
Signs and symptoms of tumour lysis syndrome in patients at risk	Baseline and as clinically indicated
24 hour urine protein in patients with worsening proteinuria	As clinically indicated
Clinical toxicity assessment of hypertension, pneumonitis, thromboembolism, diarrhea, bleeding, infection, wound healing, fatigue, GI fistula/perforation, lung, neurologic or ocular effects	At each visit

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Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

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## J - Supplementary Public Funding

### Exceptional Access Program ([EAP Website](#))

- pazopanib - For first-line treatment of advanced or metastatic renal cell carcinoma of clear cell histology in patients with good performance status (ECOG 0-1), with specific criteria

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## K - References

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Van der Graaf WTA, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379(9829):1879-86.

**December 2024** Updated Adverse Effects, Dosing, Administration Guidelines, Special Precautions, Interactions, and Monitoring sections

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## L - Disclaimer

Refer to the [New Drug Funding Program](#) or [Ontario Public Drug Programs](#) websites for the most up-to-date public funding information.

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