# Pazopanib: Drug information



(For additional information see "Pazopanib: Patient drug information ")

For abbreviations and symbols that may be used in Lexicomp (show table)

## ALERT: US Boxed Warning

**Hepatotoxicity:**

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

## Brand Names: US

Votrient

## Brand Names: Canada

Votrient

## Pharmacologic Category

Antineoplastic Agent, Tyrosine Kinase Inhibitor; Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor

## Dosing: Adult

**Renal cell carcinoma (RCC), advanced:** Oral: 800 mg once daily (Sternberg 2010)

**Soft tissue sarcoma (STS), advanced:** Oral: 800 mg once daily (Van Der Graaf 2012)

**Thyroid cancer, advanced differentiated (off-label use):** Oral: 800 mg once daily until disease progression or unacceptable toxicity (Bible 2010; Bible 2014)

*Missed doses:* If a dose is missed, do not take if <12 hours until the next dose.

*Concomitant CYP3A4 inhibitors/inducers:*

CYP3A4 inhibitors: Avoid concomitant strong CYP3A4 inhibitors (may increase pazopanib concentrations). If pazopanib must be administered concomitantly with a potent enzyme inhibitor, reduce pazopanib to 400 mg once daily with careful monitoring; further dosage reductions may be needed if adverse events occur.

CYP3A4 inducers: Avoid concomitant strong CYP3A4 inducers (may decrease pazopanib concentrations); use of pazopanib is not recommended in situations where the chronic use of a strong CYP3A4 inducer is required.

## Dosing: Geriatric

Refer to adult dosing.

## Dosing: Renal Impairment

CrCl ≥30 mL/minute: No dosage adjustment necessary (renal impairment is not expected to influence pazopanib exposure).

CrCl <30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, renal impairment is not expected to influence pazopanib exposure.

## Dosing: Hepatic Impairment

*Preexisting impairment:*

Mild (bilirubin ≤1.5 times ULN or ALT >ULN): No dosage adjustment required (Shibata 2013).

Moderate (bilirubin >1.5 to 3 times ULN): Consider alternative therapy or reduce to 200 mg once daily (maximum tolerated dose in patients with moderate hepatic impairment) (Shibata 2013).

Severe (bilirubin >3 times ULN with any ALT level): Use is not recommended.

*During treatment:*

Isolated ALT elevations 3 to 8 times ULN: Continue treatment, monitor liver function weekly until ALT returns to grade 1 or baseline.

Isolated ALT elevations >8 times ULN: Interrupt treatment until ALT returns to grade 1 or baseline. If therapy benefit is greater than the risk of hepatotoxicity, may reinitiate treatment at ≤400 mg once daily (with liver function monitored weekly for 8 weeks); permanently discontinue if ALT >3 times ULN occurs with reinitiation.

ALT >3 times ULN concurrently with bilirubin >2 times ULN: Permanently discontinue; monitor until resolution.

Gilbert syndrome with mild indirect bilirubin elevation and ALT >3 times ULN: Refer to isolated ALT elevations dosage recommendations above.

## Dosing: Adjustment for Toxicity

**Initial dosage reduction: Note:** Prior to dose reduction, temporarily discontinue therapy if 24-hour urine protein ≥3 g or for other toxicities when clinically indicated.

*RCC:* Reduce to 400 mg once daily

*STS:* Reduce to 600 mg once daily

**Further modification:** *RCC, STS:* Adjust dose in 200 mg increments or decrements based on individual tolerance; maximum dose: 800 mg

**Hypertension:** Manage as appropriate with antihypertensive therapy and interrupt treatment or reduce dose as clinically warranted.

**Hypertension (severe, persistent, and refractory to antihypertensives and dose reduction) or evidence of hypertensive crisis:** Discontinue treatment.

**Infection, serious:** Consider treatment interruption or discontinuation.

**Proteinuria (24-hour urine protein ≥3 g):** Interrupt treatment and reduce the dose.

**Proteinuria (recurrent 24-hour urine protein ≥3 g refractory to dose reduction):** Discontinue treatment.

**Pulmonary toxicity: Interstitial lung disease (ILD) or pneumonitis:** Discontinue treatment.

**Reversible posterior leukoencephalopathy syndrome (RPLS):** Permanently discontinue.

**Thrombotic microangiopathy (TMA):** Permanently discontinue.

**Wound dehiscence:** Discontinue treatment.

## Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Votrient: 200 mg

## Generic Equivalent Available (US)

No

## Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM188476.pdf, must be dispensed with this medication.

## Administration

Administer on an empty stomach, 1 hour before or 2 hours after a meal. Do not crush tablet (rate of absorption may be increased; may affect systemic exposure).

## Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

## Use

**Renal cell carcinoma, advanced:** Treatment of advanced renal cell carcinoma

**Soft tissue sarcoma, advanced:** Treatment of advanced soft tissue sarcoma (in patients who have received prior chemotherapy)

Limitations of use: The efficacy of pazopanib for the treatment of adipocytic soft tissue sarcoma or gastrointestinal stromal tumors (GIST) has not been demonstrated.

## Use: Off-Label

Thyroid cancer (advanced, differentiated)

## Medication Safety Issues

**Sound-alike/look-alike issues:**

PAZOPanib may be confused with axitinib, palbociclib, pegaptanib, PONATinib, regorafenib, SUNItinib, vandetanib

Votrient may be confused with vorinostat

**High alert medication:**

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

## Adverse Reactions

>10%:

Cardiovascular: Hypertension (40% to 42%; grade 3: 4% to 7%, early in treatment), bradycardia (2% to 19%), peripheral edema (STS: 14%), cardiac insufficiency (11% to 13%)

Central nervous system: Fatigue (19%, grade 3: 2%; STS: 65%, grades 3/4: 1% to 13%), tumor pain (STS: 29%, grade 3: 8%), headache (10%; STS: 23%, grade 3: 1%), dizziness (11%)

Dermatologic: Hair discoloration (38% to 39%, grade 3: <1%), exfoliative dermatitis (STS: 18%, grade 3: <1%), alopecia (8% to 12%), dermatological disease (STS: 11%, grade 3: 2%), hypopigmentation (STS, skin: 11%), palmar-plantar erythrodysesthesia (6% to 11%)

Endocrine & metabolic: Weight loss (9%, STS: 48%, grade 3: 4%), increased serum glucose (41% to 45%, grade 3: <1%), increased thyroid-stimulating hormone (TSH), decreased serum albumin (STS: 34%, grade 3: 1%), decreased serum phosphate (34%, grade 3: 4%), decreased serum sodium (31%, grade 3: 1% to 4%), decreased serum magnesium (26%, grades 3/4: ≤1%), decreased serum glucose (17%, grade 4: <1%), increased serum potassium (STS: 16%, grade 3: 1%)

Gastrointestinal: Diarrhea (52% to 59%; grades 3/4: ≤5%), nausea (26%, grade 3: <1%; STS: 56%, grade 3: 3%), decreased appetite (STS: 40%, grade 3: 6%), anorexia (22%, grade 3: 2%), vomiting (21%, grades 3/4: ≤2%; STS: 33%, grade 3: 3%), dysgeusia (8%, STS: 28%), increased serum lipase (27%, grades 3/4: 4%), gastrointestinal pain (STS: 23%, grade 3: 3%), abdominal pain (11%, grade 3: 2%), mucositis (STS: 12%, grade 3: 2%), stomatitis (STS: 11%, grade 3: <1%)

Hematologic & oncologic: Leukopenia (37% to 44%; STS, grade 3: 1%), lymphocytopenia (31%; grades 3/4: ≤4%; STS: 43%, grade 3: 10%), thrombocytopenia (32% to 36%; grades 3/4: ≤6%; grade 4: ≤1%), neutropenia (33% to 34%; grades 3/4 [in patients of East Asian descent]: 12%; grades 3/4 [in patients of non-East Asian descent]: ≤4%), hemorrhage (13% to 22%, including pulmonary, gastrointestinal, and genitourinary, grade 4: 1%, including intracranial, subarachnoid, and peritoneal)

Hepatic: Increased serum AST (51% to 53%; grades 3/4: ≤7%), increased serum ALT (4% to 53%;

grades 3/4: 2% to 10%), increased serum bilirubin (29% to 36%; grades 3/4: ≤3%), increased serum alkaline phosphatase (STS: 32%, grade 3: 3%)

Neuromuscular & skeletal: Musculoskeletal pain (STS: 23%, grade 3: 2%), myalgia (STS: 23%, grade 3: 2%), weakness (14%, grade 3: 3%)

Respiratory: Dyspnea (STS: 20%, grades 3/4: ≤5%), cough (STS: 17%)

Miscellaneous: Tumor pain (29%)

1% to 10%:

Cardiovascular: Chest pain (5% to 10%; STS, grade 3: 2%), left ventricular systolic dysfunction (STS: 8%), venous thrombosis (STS: 5%), ischemia (≤2%), myocardial infarction (≤2%), prolonged Q-T interval on ECG (2%), facial edema (RCC: 1%), transient ischemic attacks (RCC: 1%)

Central nervous system: Insomnia (STS: 9%), voice disorder (4% to 8%), chills (STS: 5%)

Dermatologic: Skin rash (RCC: 8%), skin depigmentation (RCC: 3%), xeroderma (STS: 6%), nail disease (STS: 5%)

Endocrine & metabolic: Hypothyroidism (4% to 8%)

Gastrointestinal: Dyspepsia (5% to 7%), anal hemorrhage (STS: 2%), gastrointestinal fistula (≤1%), gastrointestinal perforation (≤1%)

Genitourinary: Proteinuria (1% to 9%), hematuria (RCC: 4%)

Hematologic & oncologic: Oral hemorrhage (STS: 3%), rectal hemorrhage (RCC: 1%)

Ophthalmic: Blurred vision (STS: 5%)

Respiratory: Epistaxis (2% to 8%), pneumothorax (≤3%), hemoptysis (RCC: 2%)

Frequency not defined:

Cardiovascular: Decreased left ventricular ejection fraction, hypertensive crisis

Central nervous system: Reversible posterior leukoencephalopathy syndrome

Hematologic & oncologic: Hemolytic-uremic syndrome, neutropenic infection, thrombotic thrombocytopenic purpura

Hepatic: Hepatotoxicity, severe hepatotoxicity

Infection: Serious infection

Neuromuscular & skeletal: Arthralgia (RCC), muscle spasm (RCC)

<1%, postmarketing, and/or case reports: Cardiac disease, cerebral hemorrhage, cerebrovascular accident, congestive heart failure, interstitial pneumonitis, nephrotic syndrome, pancreatitis, retinal changes (tear), retinal detachment, torsades de pointes

## Contraindications

There are no contraindications listed in the manufacturer’s US labeling.

*Canadian labeling:* Hypersensitivity to pazopanib or any component of the formulation; use in pediatric patients <2 years of age (due to the antiangiogenic effects)

## Warnings/Precautions

***Concerns related to adverse effects:***

• Gastrointestinal perforation/fistula: Perforation and fistula (including fatal events) have been reported; monitor for symptoms of gastrointestinal perforation and fistula.

• Hand-foot skin reaction: Hand-foot skin reaction (HFSR) observed with tyrosine kinase inhibitors (TKIs) is distinct from hand-foot syndrome (palmar-plantar erythrodysesthesia) associated with traditional chemotherapy agents. HFSR due to TKIs is localized with defined hyperkeratotic lesions; symptoms include burning, dysesthesia, paresthesia, or tingling of the palms/soles, and generally occur within the first 2 to 4 weeks of treatment. Pressure and flexor areas may develop blisters (callus-like), dry/cracked skin, edema, erythema, desquamation, or hyperkeratosis. The incidence of hand-foot skin reaction (HFSR) is lower with pazopanib (compared to other tyrosine kinase inhibitors). Examine skin at baseline (remove calluses with pedicure prior to treatment) and with each visit; apply an emollient based moisturizer twice daily during treatment. If HSFR develops, consider changing moisturizer to a urea-based product; topical steroids may be utilized for the anti-inflammatory effect; avoid excessive friction or pressure to affected areas and avoid restrictive footwear. Temporary dose reduction or treatment interruption may be necessary (Appleby 2011).

• Heart failure: May cause new-onset or worsening of existing heart failure; baseline and periodic LVEF monitoring is recommended in patients at increased risk of heart failure (eg, prior anthracycline treatment). Concurrent hypertension may increase the risk for cardiac dysfunction. Monitor for signs/symptoms of heart failure.

• Hemorrhage: Hemorrhagic events (including fatal events) have been reported. In clinical studies, the most common events in renal cell carcinoma patients were hematuria, epistaxis, hemoptysis, and rectal hemorrhage. Epistaxis, mouth hemorrhage, and anal hemorrhage were most common in soft tissue sarcoma patients. Use is not recommended in patients with a history of hemoptysis, cerebral hemorrhage or clinically significant gastrointestinal hemorrhage within 6 months; these populations were excluded from clinical trials.

• Hepatotoxicity: **[US Boxed Warning]: Severe and fatal hepatotoxicity (transaminase and bilirubin elevations) has been observed in studies. Monitor hepatic function and interrupt treatment, reduce dose, or discontinue as recommended.** Liver function tests should be monitored at baseline; at weeks 3, 5, 7, and 9; at months 3 and 4; and as clinically necessary, then periodically (after month 4). Transaminase elevations usually occur early in the treatment course. Use is not recommended in patients with preexisting severe hepatic impairment (bilirubin >3 times ULN with any ALT level); dosage reduction is recommended for preexisting moderate hepatic impairment (bilirubin >1.5 to 3 times ULN). Mild indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert syndrome; for patients with known Gilbert syndrome (only a mild indirect bilirubin elevation) and ALT >3 times ULN, follow the dosage modification recommendations for isolated ALT elevations. Patients >65 years are at a higher risk for hepatotoxicity.

• Hypertension: May cause and/or worsen hypertension; hypertensive crisis has been observed. Blood pressure should be controlled prior to treatment initiation. Monitor frequently for hypertension; antihypertensive therapy should be used if needed. Hypertension usually occurs early in the

treatment course. Dosage reduction may be necessary for hypertension that is persistent despite management with antihypertensive therapy; discontinue for hypertensive crisis, or for severe and persistent hypertension which is refractory to dose reduction and antihypertensive therapy.

• Infections: Serious, including fatal, infections have been reported; monitor for signs and symptoms of infection. Temporarily or permanently discontinue therapy for serious infections as clinically indicated.

• Ocular toxicity: Cases of retinal detachment or tear have been reported.

• Proteinuria: Has been reported with use. Obtain baseline and periodic urinalysis and 24-hour urine protein when clinically indicated. Dosage reduction may be necessary for significant proteinuria (≥3 g/24 hours); discontinue for recurrent proteinuria.

• Pulmonary toxicity: Interstitial lung disease (ILD)/pneumonitis has been reported with pazopanib; may be fatal. Monitor for pulmonary symptoms which could indicate ILD/pneumonitis; discontinue if ILD or pneumonitis develop.

• QTc prolongation: QTc prolongation, including torsade de pointes, has been observed; use caution in patients with a history of QTc prolongation, with medications known to prolong the QT interval, or with preexisting cardiac disease. Obtain baseline and periodic ECGs; correct electrolyte (potassium, calcium, and magnesium) abnormalities prior to and during treatment.

• Reversible posterior leukoencephalopathy syndrome (RPLS): Has been reported (rarely); may be fatal. Monitor for neurological changes or symptoms (blindness, confusion, headache, lethargy, seizure, visual or neurologic disturbances). Hypertension (mild to severe) may also be present. Permanently discontinue pazopanib in patients who develop RPLS.

• Thromboembolic events: Venous and arterial thromboembolism have been reported. DVT, pulmonary embolism, angina, transient ischemic attack, MI, and ischemic stroke were observed more frequently in the pazopanib group (versus placebo) in clinical trials. Fatalities were observed. Monitor for signs/symptoms of venous thrombotic events and pulmonary embolism. Use with caution in patients with a history of or an increased risk for these events. Use in patients with recent arteriothrombotic event (within 6 months) has not been studied and is not recommended.

• Thrombotic microangiopathy: Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been observed in clinical studies. TMA has occurred with pazopanib monotherapy or when used in combination with bevacizumab or topotecan (off-label use); it typically occurs within 90 days of treatment initiation. Monitor for signs/symptoms and permanently discontinue in patients who develop TMA.

• Thyroid disorders: Hypothyroidism has been reported with use; monitor thyroid function tests.

• Wound healing complications: Vascular endothelial growth factor (VEGF) receptor inhibitors are associated with impaired wound healing. Discontinue treatment at least 7 days prior to scheduled surgery; treatment reinitiation should be guided by clinical judgment. Discontinue if wound dehiscence occurs.

***Disease-related concerns:***

• Renal impairment: Patients with mild-to-moderate renal impairment (CrCl ≥30 mL/minute) were included in trials. There are no pharmacokinetic data in patients with severe renal impairment undergoing dialysis (peritoneal and hemodialysis); however, renal impairment is not expected to

significantly influence pazopanib pharmacokinetics or exposure.

***Concurrent drug therapy issues:***

• Chemotherapy: Increased toxicity and mortality has been observed in trials evaluating concurrent use of pazopanib with other chemotherapeutic agents (pemetrexed, lapatinib). Pazopanib is not approved for use in combination with other chemotherapy.

• Drug-drug/drug-food interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

***Special populations:***

• East Asians: In an analysis of pooled clinical trials, grade 3 and 4 neutropenia, thrombocytopenia, and palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) were more frequently observed in patients of East Asian descent than in non-East Asian patients.

• Elderly: Patients >65 years of age may be at greater risk for transaminase elevations (ALT >3 time ULN). Patients ≥65 years of age experienced increased incidences of grade 3 or 4 fatigue, hypertension, decreased appetite, and transaminase elevations and are at increased risk for hepatotoxicity.

• Pediatric: Pazopanib is not approved for use in pediatric patients. Based on the mechanism of action, organ growth and maturation may be affected during early postnatal development. May potentially cause serious adverse effects on organ development, particularly in children <2 years of age.

• Pharmacogenomic variation: A pooled analysis of TA repeat polymorphism of UGT1A1 showed a statistically significant increase of hyperbilirubinemia in patients with the (TA)7/TA7 genotype (UGT1A1*28/*28), relative to the (TA)6/(TA)6 and (TA6/(TA)7 genotypes. In a large pooled analysis, grade 2 and 3 ALT elevations (ALT > 3 to <20 x ULN) were observed more frequently in patients carrying the HLA-B*57:01 allele versus non-carriers. Monitor liver function in all patients receiving pazopanib.

## Metabolism/Transport Effects

**Substrate** of BCRP, CYP1A2 (minor), CYP2C8 (minor), CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP2C8 (weak), CYP3A4 (weak), SLCO1B1, UGT1A1

## Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Amodiaquine: CYP2C8 Inhibitors may increase the serum concentration of Amodiaquine. *Risk X: Avoid combination*

Antacids: May decrease the serum concentration of PAZOPanib. Management: Avoid the use of antacids in combination with pazopanib whenever possible. Separate doses by several hours if antacid treatment is considered necessary. The impact of dose separation has not been investigated. *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

ARIPiprazole: CYP3A4 Inhibitors (Weak) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy and/or indication. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

AtorvaSTATin: May enhance the hepatotoxic effect of PAZOPanib. AtorvaSTATin may increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCRP/ABCG2 Inhibitors: May increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Bisphosphonate Derivatives: Systemic Angiogenesis Inhibitors may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of PAZOPanib. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of PAZOPanib. Management: Avoid concurrent use of pazopanib with strong inhibitors of CYP3A4 whenever possible. If it is not possible to avoid such a combination, reduce pazopanib adult dose to 400 mg. Further dose reductions may also be required. *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Grapefruit Juice: May increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

H2-Antagonists: May decrease the serum concentration of PAZOPanib. Management: Avoid the use of histamine H2-antagonists in combination with pazopanib. Strategies to minimize the expected interaction between these agents (eg, dose separation) have not been investigated. *Risk X: Avoid combination*

Highest Risk QTc-Prolonging Agents: Moderate Risk QTc-Prolonging Agents may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

HMG-CoA Reductase Inhibitors: May enhance the hepatotoxic effect of PAZOPanib. Specifically, the risk for increased serum transaminase concentrations may be increased. Management: Simvastatin is specifically implicated in the interaction. There is a lack of data regarding risk with other statins, but caution appears warranted with any statins. Atorvastatin should be avoided due to P-gp inhibition. **Exceptions:** AtorvaSTATin. *Risk C: Monitor therapy*

HYDROcodone: CYP3A4 Inhibitors (Weak) may increase the serum concentration of HYDROcodone. *Risk C: Monitor therapy*

Hydroxychloroquine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Irinotecan Products: UGT1A1 Inhibitors may increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be increased. UGT1A1 Inhibitors may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Ivabradine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Lapatinib: May enhance the QTc-prolonging effect of PAZOPanib. Lapatinib may increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lomitapide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Lomitapide. Management: Patients on lomitapide 5 mg/day may continue that dose. Patients taking lomitapide 10 mg/day or more should decrease the lomitapide dose by half. The lomitapide dose may then be titrated up to a max adult dose of 30 mg/day. *Risk D: Consider therapy modification*

MiFEPRIStone: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Moderate Risk QTc-Prolonging Agents: May enhance the QTc-prolonging effect of other Moderate Risk QTc-Prolonging Agents. Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

NiMODipine: CYP3A4 Inhibitors (Weak) may increase the serum concentration of NiMODipine. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Pimozide: CYP3A4 Inhibitors (Weak) may increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Probucol: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Promazine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Proton Pump Inhibitors: May decrease the serum concentration of PAZOPanib. *Risk X: Avoid combination*

QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying): May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider

an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vinflunine: PAZOPanib may enhance the adverse/toxic effect of Vinflunine. *Risk C: Monitor therapy*

Xipamide: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

**Food Interactions** Systemic exposure of pazopanib is increased when administered with food (AUC twofold higher with a meal). Grapefruit juice may increase the levels/effects of pazopanib. Management: Take on an empty stomach 1 hour before or 2 hours after a meal. Maintain adequate nutrition and hydration, unless instructed to restrict fluid intake. Avoid grapefruit/grapefruit juice.

**Pregnancy Risk Factor** D (show table)

**Pregnancy Implications** Adverse effects were observed in animal reproduction studies. Based on its mechanism of action, pazopanib would be expected to cause fetal harm if administered to a pregnant woman. Women of reproductive potential should avoid becoming pregnant during treatment and use effective contraception during therapy and for at least 2 weeks after the last pazopanib dose.

**Breast-Feeding Considerations** It is not known if pazopanib is excreted in breast milk. Because

of the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made to discontinue breast-feeding or the drug, taking into account the importance of treatment to the mother.

**Dietary Considerations** Avoid grapefruit juice.

**Monitoring Parameters** Monitor liver function tests at baseline; at weeks 3, 5, 7, and 9; at months 3 and 4; and as clinically necessary, then periodically after month 4 (monitor more frequently if clinically indicated); serum electrolytes (eg, calcium, magnesium, potassium); urinalysis (for proteinuria; baseline and periodic), 24-hour urine protein (if clinically indicated); thyroid function (TSH and $T_4$ at baseline and TSH every 6 to 8 weeks during treatment [Appleby 2011]); blood pressure; ECG (baseline and periodic); LVEF (if at risk for cardiac dysfunction; baseline and periodic); signs/symptoms of gastrointestinal perforation or fistula, venous/arterial thrombotic events, pulmonary embolism, interstitial lung disease (ILD)/pneumonitis, infection, heart failure, or neurological changes.

**Mechanism of Action** Tyrosine kinase (multikinase) inhibitor; limits tumor growth via inhibition of angiogenesis by inhibiting cell surface vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), platelet-derived growth factor receptors (PDGFR-alpha and -beta), fibroblast growth factor receptor (FGFR-1 and -3), cytokine receptor (cKIT), interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms)

## Pharmacodynamics/Kinetics

Protein binding: >99%

Metabolism: Hepatic; primarily via CYP3A4, minor metabolism via CYP1A2 and CYP2C8

Bioavailability: Rate and extent of bioavailability are increased with food and increased if tablets are crushed (do not crush tablets)

Half-life elimination: ~31 hours

Time to peak, plasma: 2 to 4 hours

Excretion: Feces (primarily); urine (<4%)

## Pricing: US

**Tablets** (Votrient Oral)

200 mg (120): $12862.50

**Disclaimer:** The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

**International Brand Names** Votirent (KW); Votrient (AE, AR, AT, AU, BE, BR, CH, CL, CR, CY, CZ, DE, DK, EE, ES, FR, GB, GT, HK, HN, HR, ID, IE, IL, IN, IS, JP, KR, LB, LK, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, QA, RO, SA, SE, SG, SK, SV, TH, TR); Votrieny (DO); Votriyent (UA); Vottrient (SI)

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