PDR.net

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Votrient

(Pazopanib) - GlaxoSmithKline

BOXED WARNING

Severe and fatal hepatotoxicity reported; monitor hepatic function and interrupt, reduce, or d/c dosing as recommended.

THERAPEUTIC CLASS

Tyrosine kinase inhibitor

DEA CLASS

RX

INDICATIONS

Treatment of advanced renal cell carcinoma (RCC). Treatment of advanced soft tissue sarcoma (STS) that has been treated with prior chemotherapy.

ADULT DOSAGE

Adults: Usual: 800mg qd without food (at least 1 hr ac or 2 hrs pc). Max: 800mg. Dose Modification: RCC: Initial dose reduction should be 400mg, and additional decrease or increase in dose should be in 200mg steps based on tolerability. STS: Decrease or increase should be in 200mg steps based on tolerability. Moderate Hepatic Impairment: Consider alternative therapy or reduce to 200mg/day. Concomitant Strong CYP3A4 Inhibitors (eg, Ketoconazole, Ritonavir, Clarithromycin): Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. If coadministration is warranted, reduce to 400mg. Further dose reductions may be needed if adverse effects occur during therapy. Missed Dose: If a dose is missed, do not take if <12 hrs until the next dose.

HOW SUPPLIED

Tab: 200mg

WARNINGS/PRECAUTIONS

Avoid with preexisting severe hepatic impairment (total bilirubin >3X ULN with any level of ALT). QT prolongation and torsades de pointes reported. Cardiac dysfunction (eg, decreased left ventricular ejection fraction [LVEF], congestive heart failure [CHF]) reported; perform baseline and periodic evaluation of LVEF in patients at risk for cardiac dysfunction (eg, previous anthracycline exposure). Hemorrhagic events reported; avoid with history of hemoptysis, cerebral, or clinically significant GI hemorrhage in the past 6 months. Arterial thromboembolic events reported; caution in patients at increased risk for these events or who have had a history of these events and avoid use if an arterial thromboembolic event has occurred within the past 6 months. Venous thromboembolic events (VTE) (eg, pulmonary embolism [PE]) and GI perforation/fistula reported. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), reported; permanently d/c in patients developing TMA. Reversible posterior leukoencephalopathy syndrome (RPLS) reported; permanently d/c in patients developing RPLS. HTN and hypertensive crisis reported; d/c if evidence of hypertensive crisis or if HTN is severe and persistent despite antihypertensive therapy and dose reduction. May impair wound healing; d/c therapy with wound dehiscence and at least 7 days prior to scheduled surgery. Hypothyroidism reported. Proteinuria reported; interrupt therapy and reduce dose for 24-hr urine protein ≥3g; d/c for repeat episodes despite dose reductions. Serious infections reported; institute appropriate anti-infective therapy promptly and consider interruption or discontinuation if serious infections develop. May cause serious adverse effects on organ development in pediatric patients; not for use in pediatric patients. May cause fetal harm if used during pregnancy.

ADVERSE REACTIONS

Hepatotoxicity, diarrhea, HTN, hair color changes, N/V, anorexia, fatigue, asthenia, headache, weight/appetite decreased, tumor pain, dysgeusia, dyspnea, musculoskeletal pain, skin hypopigmentation.

DRUG INTERACTIONS

See Dosage. Avoid with drugs that raise gastric pH (eg, proton pump inhibitors [PPIs]); if such drugs are needed, consider short-acting antacids in place of PPIs and H_2 receptor antagonists; separate antacid and pazopanib dosing by several hrs. Do not use in combination with other cancer therapy; increased toxicity and mortality reported with pemetrexed and lapatinib. Strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin) may increase concentrations; avoid use and consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4, or reduce dose of pazopanib when it must be coadministered. Avoid grapefruit or grapefruit juice. CYP3A4 inducers (eg, rifampin) may decrease plasma concentrations; consider an alternate concomitant medication with no or minimal enzyme induction potential and avoid pazopanib if chronic use of strong CYP3A4 inducers cannot be avoided. Avoid use with strong inhibitors of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), and consider alternative concomitant medicinal products with no or minimal potential to inhibit P-gp or BCRP. Not recommended with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8. Simvastatin may increase incidence of ALT elevations; follow pazopanib dosing guidelines or consider alternatives to pazopanib or consider discontinuing simvastatin. Caution in patients taking antiarrhythmics or other medications that may prolong the QT interval.

PREGNANCY

Category D, not for use in nursing.

MECHANISM OF ACTION

Tyrosine kinase inhibitor; inhibits vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor

receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms).

PHARMACOKINETICS

Absorption: T_{max}=2-4 hrs (median); (800mg dose) AUC=1037mcg•hr/mL, C_{max}=58.1mcg/mL. **Distribution:** Plasma protein binding (>99%). **Metabolism:** CYP3A4 (major), CYP1A2/CYP2C8 (minor). **Elimination:** Feces (primary), urine (<4% administered dose); (800mg dose) $T_{1/2}$=30.9 hrs.

ASSESSMENT

Assess for history of QT interval prolongation, cardiac disease, severe hepatic impairment, pregnancy/nursing status, and for possible drug interactions. Assess for history of hemoptysis/cerebral or clinically significant GI hemorrhage, or an arterial thromboembolic event in the past 6 months. Assess if patient is planning to undergo any surgical procedure. Assess thyroid function. Obtain baseline BP, LFTs, ECG, electrolytes, and urinalysis. Obtain baseline LVEF in patients at risk of cardiac dysfunction.

MONITORING

Monitor for signs/symptoms of hepatotoxicity, QT prolongation, torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial thromboembolic events, VTE, TMA, TTP, HUS, PE, RPLS, GI perforation or fistula, HTN/hypertensive crisis, impaired wound healing, proteinuria, infections, and other adverse reactions. Monitor BP early after starting treatment and then frequently to ensure BP control. Perform periodic urinalysis with follow-up measurement of 24-hr urine protein as clinically indicated. Monitor ECG, thyroid function tests, and serum electrolytes. Monitor LFTs at Weeks 3, 5, 7, and 9, at Months 3 and 4, as clinically indicated, and continue periodic monitoring after Month 4. Periodically monitor LVEF in patients at risk of cardiac dysfunction.

PATIENT COUNSELING

Advise that lab monitoring will be required prior to and while on therapy. Instruct to report any signs/symptoms of liver dysfunction, HTN, CHF, unusual bleeding, arterial thrombosis, new onset of dyspnea, chest pain, localized limb edema, GI perforation/fistula, infection, and worsening of neurologic function consistent with RPLS (eg, headache, seizure, lethargy, confusion, blindness). Advise to d/c treatment at least 7 days prior to a scheduled surgery. Inform that thyroid function testing and urinalysis will be performed during treatment. Advise on how to manage diarrhea and to notify healthcare provider if moderate to severe diarrhea occurs. Advise women of childbearing potential to avoid becoming pregnant during therapy. Advise to inform healthcare provider of all concomitant medications, vitamins, or dietary and herbal supplements. Advise that depigmentation of the hair or skin may occur during treatment. Instruct that if a dose is missed, to not take if it is <12 hrs until the next dose.

ADMINISTRATION/STORAGE

Administration: Oral route. Do not crush tabs. Take without food (at least 1 hr ac or 2 hrs pc). **Storage:** 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).