PRODUCT MONOGRAPH

Pr VOTRIENT®

Pazopanib (as pazopanib hydrochloride)

Tablets, 200 mg and 400 mg

Antineoplastic Agent

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Date of Revision:
July 30, 2015

Submission Control No: 185245

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Pazopanib (as pazopanib hydrochloride) tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets / 200 mg, 400 mg	None. *For a complete listing see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

RENAL CELL CARCINOMA
VOTRIENT (pazopanib hydrochloride) is indicated for the treatment of patients with metastatic renal cell (clear cell) carcinoma (mRCC) as first-line systemic therapy or as second-line systemic therapy after treatment with cytokines for metastatic disease.

Approval of VOTRIENT in mRCC is based on significant progression-free survival benefit in patients with mRCC of good performance status (ECOG 0-1). Prolongation of overall survival was not demonstrated nor were quality-of-life differences shown between patients receiving VOTRIENT versus placebo in the pivotal phase III trial (see PART II, CLINICAL TRIALS).

SOFT TISSUE SARCOMA (STS)
VOTRIENT (pazopanib hydrochloride) is indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

Patients were required to have disease progression on or after, or be intolerant to, an anthracycline-based regimen in the pivotal phase III study in STS.

The pivotal phase III study in STS was designed to assess VOTRIENT in patients with selected tumour types including: fibroblastic, so-called fibrohistiocytic, leiomyosarcoma, malignant glomus tumours, skeletal muscles, vascular, uncertain differentiation (excluding chondrosarcoma, Ewing tumours / primitive neuroectodermal tumours), malignant peripheral nerve sheath tumours, and undifferentiated soft tissue sarcomas not otherwise specified. However not all of the listed tumour types have been assessed in the clinical study (see CLINICAL TRIALS).

The efficacy and safety of VOTRIENT for the treatment of patients with other STS subtypes, including adipocytic STS (liposarcoma) and gastrointestinal stromal tumours (GIST), have not been demonstrated (see WARNINGS AND PRECAUTIONS and CLINICAL TRIALS).

Clinical effectiveness of VOTRIENT in STS is based on significant progression-free survival benefit in patients with advanced STS. Prolongation of overall survival was not demonstrated nor were quality-of-life differences shown between patients receiving VOTRIENT versus placebo in the pivotal phase III trial (see Part II, CLINICAL TRIALS).

Geriatrics (65 years of age and over):

In clinical trials with VOTRIENT for the treatment of mRCC, 196 patients (33%) were aged ≥65 years, and 34 patients (6%) were aged >75 years. In the STS clinical trials, 93 patients (24%) were aged ≥65 years, and 17 subjects (4%) were aged ≥75 years. No overall differences in safety or effectiveness of VOTRIENT were observed between these patients and younger patients in clinical trials. However, a meta-analysis shows that patients over 60 years of age may be at greater risk for ALT >3 X ULN. Although no other differences in responses between elderly and younger patients have been identified clinically; a greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (Less than 18 years of age):

The safety and efficacy of pazopanib in children have not been established (see WARNINGS AND PRECAUTIONS). Toxicology studies in rodents showed hypertrophy of epiphyseal growth plates and abnormalities in growing incisors and severe effects on body weight gain, organ growth and organ maturation during early post-natal development (see PART II, TOXICOLOGY). VOTRIENT is not recommended for use in children and is contraindicated in children less than 2 years of age (see CONTRAINDICATIONS).

CONTRAINDICATIONS

VOTRIENT (pazopanib hydrochloride) is contraindicated for:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section of the product monograph.

- Pediatric patients less than 2 year of age. VOTRIENT is an anti-angiogenic agent that severely affects body weight gain, organ growth and organ maturation during early post-natal development in rats (see WARNINGS AND PRECAUTIONS, TOXICOLOGY).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

VOTRIENT tablets should be prescribed by a physician experienced in the administration of anti-cancer agents.

Monitor hepatic function (see Monitoring and Laboratory Tests section below) **and interrupt, reduce or discontinue dosing as recommended** (see Hepatic section below)**.** VOTRIENT should not be used in patients who have baseline plasma bilirubin concentrations > 1.5 X ULN (with direct bilirubin >35%) and ALT elevations of >2 X ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). Patients over 60 years of age may be at greater risk for ALT >3 X ULN. See Hepatic section below and DOSAGE AND ADMINISTRATION, Hepatic Impairment.

The following are clinically significant adverse events:

- Hepatotoxicity, including fatalities (see Hepatic section below)
- Hypertension, including hypertensive crisis (see Cardiovascular section below)
- Cardiac Dysfunction (see Cardiovascular section below)
- QT/QTc prolongation (see Cardiovascular section below)
- Arterial and Venous Thrombotic Events and Thrombotic Microangiopathy (see Cardiovascular section below)
- Hemorrhage (see Hemorrhagic section below)
- Gastrointestinal Perforation and Fistula (see Gastrointestinal section below)
- Posterior Reversible Encephalopathy Syndrome (PRES/Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (see Neurologic section below)

General

Drug-Drug Interactions: Co-administration of VOTRIENT with strong inhibitors of CYP3A4 or P-glycoprotein (PgP) should be avoided as should co-administration with inhibitors that simultaneously target PgP, the Breast Cancer Resistance Protein (BCRP) and/or CYP3A4. These inhibitors may increase pazopanib concentrations (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS) and drug toxicity. Co-administration with inducers of CYP3A4 or PgP or drugs that raise gastric pH should be avoided due to the risk of reduced effectiveness of the drug.

Combination with other systemic anti-cancer therapies: Clinical trials of VOTRIENT in combination with pemetrexed (non-small cell lung cancer (NSCLC)) and lapatinib (cervical cancer) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens. VOTRIENT is not indicated for use in combination with other anti-cancer agents.

Soft Tissue Sarcoma Tumour Types: Only patients with selective histological subtypes of STS were allowed to participate in the studies, therefore efficacy and safety of VOTRIENT can only be considered established for those subgroups of STS and treatment with VOTRIENT should be restricted to such STS subtypes (see INDICATIONS and Clinical Trials).

The following tumour types were excluded in the STS Phase III clinical trial: adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumours/primitive neuroectodermal tumours, GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.

Patients with adipocytic sarcoma (liposarcoma) were excluded from the pivotal phase III study, since in a phase II study (VEG20002), activity (PFS at week12) observed with VOTRIENT in adipocytic tumours was indeterminant (see CLINICAL TRIALS). Patients with the other tumour types listed above were excluded due to the unique pathogenesis and treatment options for these tumour types.

The pivotal phase III study excluded patients who have been previously treated with inhibitors of angiogenesis and/or VEGF or VEGFR-targeting agents.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with VOTRIENT have not been conducted. However, proliferative lesions were found in mice treated with VOTRIENT. Genotoxicity studies showed no evidence of clastogenic or mutagenic activity (see PART II, TOXICOLOGY; Carcinogenesis, Mutagenesis, Impairment of Fertility).

Cardiovascular

Hypertension: Hypertension is a common adverse event in patients treated with VOTRIENT and blood pressure should be well controlled prior to initiating treatment with VOTRIENT. Patients were required to have diastolic BP ≤ 90 mm Hg and systolic BP ≤ 140 mm Hg for entry into the controlled phase III trial. During therapy patients should be monitored for hypertension early after starting treatment (no longer than one week after starting VOTRIENT) and frequently thereafter to ensure blood pressure control, and treated promptly with a combination of standard anti-hypertensive therapy and VOTRIENT dose reduction or interruption as clinically warranted (see DOSAGE AND ADMINISTRATION).

In controlled clinical studies with VOTRIENT for the treatment of RCC and STS, approximately 40% of patients who received VOTRIENT compared with 6% and 10% of patients, respectively, on placebo experienced hypertension. Grade 3 hypertension was reported in 4% and 7% in those receiving VOTRIENT compared with 0.7% on placebo. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurred early in the course of VOTRIENT treatment (approximately 40% of cases occurred by Day 9 and approximately 90% of cases occurred in the first 18 weeks). The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reduction with (0.7%) permanently discontinuing treatment with VOTRIENT.

Hypertensive crisis was originally reported with VOTRIENT in the overall safety population for mRCC (1/586). Additional reports of hypertensive crisis have been received from the overall VOTRIENT clinical development program. These events have occurred in patients with or without a history of hypertension.

Patients with hypertension that is not controlled by medications should not be treated with VOTRIENT. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and VOTRIENT dose reduction.

Cardiac Dysfunction: In three clinical trials with VOTRIENT for mRCC, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. In the overall safety population for mRCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%). LVEF was not monitored in these clinical studies for mRCC; however the rates of cardiac dysfunction were similar between the placebo and VOTRIENT arms. In a separate randomised mRCC trial of VOTRIENT compared with sunitinib, cardiac dysfunction was defined as symptoms of cardiac dysfunction or ≥15% absolute decline in LVEF compared with baseline or a decline in LVEF of ≥10% compared with baseline that is also below the lower limit of normal. In patients who had baseline and follow-up LVEF measurements, cardiac dysfunction occurred in 13% (47/362) of patients on VOTRIENT compared to 11% (42/369) of patients on sunitinib. Congestive heart failure was observed in 0.5% of patients on each arm. In the phase III STS clinical trial, congestive heart failure was reported in 3 out of 240 patients (1%). In this trial, decreases in LVEF in patients who had post-baseline measurement were detected in 11% (16/142) in the VOTRIENT arm

compared with 5% (2/40) in the placebo arm. Fourteen of the 16 patients in the VOTRIENT arm had concurrent hypertension. VOTRIENT has not been studied in patients with moderate to severe heart failure or a below normal LVEF.

Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction including those who have received prior anthracyclines. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment).

QT Prolongation and Torsade de Pointes: In clinical studies for VOTRIENT in mRCC and STS patients, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 1.0% of mRCC patients (3/290) and <1% of STS patients (1/240) compared with no patients on placebo. Torsade de Pointes occurred in 2/586 (0.3%) patients who received VOTRIENT in the mRCC clinical studies. VOTRIENT should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease (including myocardial ischemia and congestive heart failure). Other risk factors for Torsade de Pointes include diabetes mellitus, autonomic neuropathy and electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia). When using VOTRIENT, baseline and periodic monitoring of electrocardiograms should be performed and electrolytes should be maintained within the normal range.

Decreased Heart Rate: In a placebo controlled cardiac conduction study in patients with solid tumours (N=65), VOTRIENT treatment resulted in decreased heart rate compared to placebo treatment (see DRUG INTERACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Cardiovascular). Symptomatic bradycardia was reported rarely (<0.1%) based on a review of the pazopanib clinical trial safety database. VOTRIENT should be used with caution in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV block), ischemic heart disease, or congestive heart failure. Medicinal products that result in a decrease in heart rate should be used with caution if administered concomitantly with VOTRIENT.

Arterial Thrombotic Events: In clinical studies for VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed, some of which were fatal. In the controlled phase III RCC and STS studies, these events were observed more frequently in patients treated with VOTRIENT in the RCC trial 9/290 (3%) and in the STS trial 5/240 (2%) while none were observed in patients receiving placebo. The events included myocardial infarction/ischemia 5/290 (1.7%) and 4/240 (2%); cerebral vascular accident 1/290 (0.3%) and 1/240 (0.4%); and transient ischemic attack 4/290 (1.4%) and none, in the RCC and the STS trials, respectively). Fatal arterial thrombotic events occurred in 2/290 (0.7%, ischemic stroke and myocardial ischemia) of patients treated with VOTRIENT and none receiving placebo in the RCC trial. No fatal arterial thrombotic events occurred in the STS trial. VOTRIENT should be used with

caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months and should not be used in these patients.

Venous Thromboembolic Events: In clinical studies with VOTRIENT, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. The incidence was higher in the STS population (5 %) than in the RCC population (2 %). In the pivotal trial in the STS population, the incidences of venous thromboembolic events were 5% in patients treated with VOTRIENT compared with 2% with placebo. In the pivotal clinical trial in the mRCC population, the incidences of venous thromboembolic events were 1% in patients treated with VOTRIENT compared with 1% with placebo. Monitor for signs and symptoms of venous thromboembolic events and pulmonary embolism.

Thrombotic Microangiopathy: Thrombotic microangiopathy (TMA) [including cases identified as thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS)] has been reported in clinical trials and in post-marketing experience of VOTRIENT as monotherapy in combination with bevacizumab (see Adverse Reactions, Clinical Trial Adverse Drug Reactions Post-marketing Adverse Reactions). Permanently discontinue VOTRIENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued consistent with a role reported for inhibitors of the VEGF pathway in this event. VOTRIENT is not indicated for use in combination with other agents.

Endocrine and Metabolism

Hypothyroidism: In clinical studies with VOTRIENT, events of hypothyroidism have occurred. Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm in the mRCC trial and in 19 patients (8 %) treated with VOTRIENT and no patients (0%) for placebo in the STS trial.

Proactive monitoring of thyroid function tests is recommended.

Gastrointestinal

Gastrointestinal Perforations and Fistula: In clinical studies for VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred, some of which were fatal. In the RCC and STS trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586) of patients and 1% (4/382) of patients receiving VOTRIENT, respectively. Fatal perforations occurred in 0.3% (2/586) of these patients in the RCC trials and in 0.3% (1/382) of these patients in the STS trials. VOTRIENT should be used with caution in patients at risk for GI perforation or fistula. Monitor for signs and symptoms of gastrointestinal perforation or fistula.

Hemorrhagic

In clinical studies with VOTRIENT, hemorrhagic events have been reported, some of which were fatal. In the controlled clinical study with VOTRIENT for the treatment of mRCC, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. In the overall safety populations for mRCC (N=586), cerebral hemorrhage was observed in <1% of patients treated with VOTRIENT and fatal hemorrhage occurred in 0.9% patients.

In a clinical trial of VOTRIENT for the treatment of STS, 53/240 (22%) of patients treated with VOTRIENT compared to 10/123 (8%) treated with placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were epistaxis (8%), mouth hemorrhage (3%), and anal hemorrhage (2%). Grade 4 hemorrhagic events occurred in 1% (3/240) of patients and included intracranial hemorrhage, subarachnoid hemorrhage and peritoneal hemorrhage.

VOTRIENT has not been studied in patients who had a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months. Treatment with VOTRIENT is not recommended if there is a history of hemoptysis, cerebral or clinically significant gastrointestinal bleeding in the past 6 months, and VOTRIENT should be used with caution in patients with a significant risk of hemorrhage.

Hepatic

Hepatic Effects: Cases of hepatic failure (including fatalities) have been reported during use of VOTRIENT. In clinical trials with VOTRIENT that supported initial mRCC approval, increases in serum transaminases [ALT, aspartate aminotransferase (AST)] and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Based on a meta-analysis, patients over 60 years of age may be at greater risk for ALT >3 X ULN. The vast majority (over 90 %) of all transaminase elevations of any grade occurred in the first 18 weeks. Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

In the controlled phase III clinical study with VOTRIENT for the treatment of mRCC, ALT >3x ULN was reported in 18% and 3% of patients who received VOTRIENT and placebo, respectively. ALT >10x ULN was reported in 4% of patients who received VOTRIENT and in <1% of placebo patients. Concurrent elevation in ALT >3x ULN and bilirubin >2x ULN in the absence of significant alkaline phosphatase elevation occurred in 1% of patients on VOTRIENT and <1% on placebo. In patients who discontinued study treatment due to an adverse event, hepatic related effects were the most common reasons for study discontinuation in the phase III controlled clinical trial (4%) and in the phase II single-arm study (4%).

In a controlled clinical trial of VOTRIENT for the treatment of STS, ALT >3 X ULN was reported in 18% and 5% of the VOTRIENT and placebo groups, respectively. ALT > 8 X ULN was reported in 7% and 2% of the VOTRIENT and placebo groups, respectively. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 4/240 (2%) of patients on VOTRIENT and 1/123 (<1%) on placebo.

One third of a percent (0.3%) of the patients (2/586) from trials that supported the RCC indication died with disease progression and hepatic failure, and 0.4% of patients (1/240) in the STS trial died of hepatic failure.

Monitor serum liver tests before initiation of treatment with VOTRIENT, at weeks 2, 4, 6 and 8, at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4. Physicians should inform patients on the possible signs and symptoms of hepatic dysfunction (including jaundice, unusual darkening of the urine, anorexia, nausea, fatigue, right upper abdominal discomfort and vomiting) so appropriate management can be implemented to minimize this impact.

The following guidelines are provided for patients with baseline values of total bilirubin ≤ 1.5 X ULN and AST and ALT ≤ 2 X ULN.

- Patients with isolated ALT elevations between 3 X ULN and ≤8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE) or baseline.
- Patients with ALT of >8 X ULN should have VOTRIENT interrupted until they return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit for reinitiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks (see DOSAGE AND ADMINISTRATION). Following reintroduction of VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently discontinued.
- If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.
- For isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) treatment could continue and dose modification is not required. However, further evaluation for a possible underlying cause should be considered.

Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations (see Drug-Drug Interactions) and should be undertaken with caution and close monitoring. In addition, caution and close monitoring should be undertaken with concomitant use of VOTRIENT and other statins as there are currently insufficient data available to assess their impact on ALT levels.

Hepatic Impairment: In a phase I hepatic impairment study, patients with moderate hepatic impairment at baseline experienced dose limiting toxicity at 400 mg (half the recommended daily dose). VOTRIENT should not be used in patients with baseline plasma bilirubin concentrations > 1.5 X ULN (with direct bilirubin > 35%) and ALT elevations of > 2 X ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). VOTRIENT should be used with caution in patients with mild hepatic impairment as no formal studies have been carried out in this patient population.

Infections

Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of VOTRIENT for serious infections.

Ophthalmologic

In the post-marketing setting, cases of non-exudative retinal detachment have been reported in patients treated with VOTRIENT. Reports indicated that, after treatment, many cases of retinal detachment resolved and therapy with VOTRIENT was continued or resumed; however, recurrence has been noted.

Neurological

Posterior reversible encephalopathy syndrome (PRES) /Reversible Posterior Leukoencephalopathy Syndrome (RPLS): PRES/RPLS has been reported in patients receiving VOTRIENT and may be fatal. There was a history or new onset of hypertension, often severe, at the time of the event in all reports. PRES/RPLS occurred within 90 days of initiating VOTRIENT.

PRES/RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may not be present in all cases of PRES/RPLS. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging. Permanently discontinue VOTRIENT in patients developing PRES/RPLS.

Peri-Operative Considerations

Wound Healing: No formal studies on the effect of VOTRIENT on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgement of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence.

Renal

Proteinuria: In clinical studies with VOTRIENT proteinuria and nephrotic syndrome have been reported. In the controlled phase III clinical study with VOTRIENT for the treatment of mRCC, proteinuria was reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In the controlled clinical trial for the treatment of STS, proteinuria was reported in 1% of patients treated with VOTRIENT and in 3% treated with placebo. One patient (1/240, 0.4%) treated with VOTRIENT experienced nephrotic syndrome and was withdrawn from treatment. Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria with measurement of 24-hour urine protein as clinically indicated. Interrupt VOTRIENT and dose reduce for 24-hour urine protein ≥3 grams; discontinue VOTRIENT for repeat episodes despite dose reductions. VOTRIENT should be discontinued if the patient develops nephrotic syndrome. Patients with > 1 g protein (24 h collection) at baseline were excluded from clinical studies.

Reproduction

VOTRIENT may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed (see PART II, TOXICOLOGY).

Respiratory

Pneumothorax: In the mRCC and STS pivotal trials, pneumothorax was seen in patients treated with VOTRIENT and in no patients in the placebo groups. All patients with pneumothorax had lung metastases at baseline.

Interstitial Lung Disease (ILD)/Pneumonitis: Cases of ILD/pneumonitis, including fatalities, have been reported in association with VOTRIENT. Ground glass opacities were detected in some patients upon CT scan, with some patients presenting with symptoms such as dyspnea, cough or fever. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue VOTRIENT in patients developing ILD or pneumonitis. Advise patients to promptly report any new or worsening respiratory symptoms.

Special Populations

Ethnicity: Neutropenia, thrombocytopenia and palmar-plantar erythrodysaethesia syndrome were observed more frequently in patients of East Asian descent.

Pregnant Women: Pre-clinical studies in animals have shown that pazopanib was teratogenic, embryotoxic, fetotoxic and abortifacient (see PART II TOXICOLOGY). Clinical trials have not been conducted in pregnant women.

VOTRIENT may cause fetal harm when administered to pregnant women. If VOTRIENT is used during pregnancy, or if the patient becomes pregnant while receiving VOTRIENT, the potential hazard to the fetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT and for up to 8 weeks after ending treatment.

Nursing Women: The safe use of VOTRIENT during lactation has not been established. It is not known whether VOTRIENT is excreted in human milk. Breastfeeding should be discontinued during treatment with VOTRIENT.

Pediatrics: The safety and efficacy of VOTRIENT in children less than 18 years of age have not been established. Toxicology studies in rodents showed hypertrophy of epiphyseal growth plates and abnormalities in growing incisors. In addition, a juvenile toxicity study in rats aged 9 to 14 days post-partum dosed at 10 and 100 mg/kg/day (equal to approximately 0.16x and 0.43x human clinical exposure based on AUC in adults, respectively) showed profound effects on organ growth and maturation, including decreased organ weights and glomerulopathy. A dose level of 10 mg/kg/day resulted in severely decreased body weight gain. A dose level of 100 mg/kg/day resulted in deaths, a lack of body weight gain, and decreased cell proliferation and increased cell apoptosis in various organs (see PART II, TOXICOLOGY).

VOTRIENT is not recommended for use in children less than 18 years of age. VOTRIENT is contraindicated in children younger than 2 years of age (see PART I, CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Prior to treatment and during the course of therapy with VOTRIENT patients should be monitored for hypertension and standard anti-hypertensive therapy should be initiated as required. Normal blood pressure (diastolic $\leq$ 90 mm Hg and systolic $\leq$ 140 mm Hg), confirmed by two measurements separated by 24 hours, should be recorded for patients prescribed anti-hypertensive medication prior to treatment with VOTRIENT. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction including those who have received prior anthracyclines.

ECG evaluations should be performed at baseline and periodically during treatment with VOTRIENT to monitor for decreased heart rate and ECG intervals (see ACTION AND CLINICAL PHARMACOLOGY, Cardiovascular).

When using VOTRIENT, complete blood counts (CBC), clinical chemistries [including blood glucose, lipase/amylase, creatinine and electrolytes (calcium, magnesium, potassium, phosphate and sodium)], urinalyses and electrocardiograms should be measured at baseline and periodically during treatment.

Proactive monitoring of thyroid function tests is recommended.

Monitor serum liver tests before initiation of treatment with VOTRIENT at weeks 2, 4, 6, and 8, at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4 (see WARNINGS AND PRECAUTIONS; Hepatic Effects, and Hepatic Impairment).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of VOTRIENT has been evaluated in more than 1600 patients in clinical trials including 977 patients in the monotherapy studies which include 586 mRCC patients. The mRCC data described below reflect exposure to VOTRIENT in 290 mRCC patients who participated in a randomized, double-blind, placebo-controlled study (VEG105192). The median duration of treatment was 7.4 months for patients who received VOTRIENT and 3.8 months for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption and thirty-six percent (36%) required a dose reduction.

The safety and efficacy of VOTRIENT in soft tissue sarcoma (STS) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study (VEG110727). Patients (N = 369) with advanced STS who had received prior anthracycline treatment, or were unsuited for such therapy, were randomized to receive VOTRIENT 800 mg once daily (N = 246) or placebo (N = 123). The median duration of treatment was 4.5 months for the VOTRIENT arm and 1.9 months for the placebo arm.

Clinical Trial Adverse Drug Reactions

Potentially serious adverse reactions with VOTRIENT included hepatic effects, hypertension, QT prolongation and Torsade de Pointes, arterial and venous thrombotic events, cardiac dysfunction, hemorrhagic events and gastrointestinal perforation and fistula (see WARNINGS AND PRECAUTIONS). Other important serious adverse reactions identified in STS trials included venous thromboembolic events and pneumothorax.

Metastatic Renal Cell Carcinoma

Table 1 presents the most common adverse reactions occurring in ≥ 10 % of patients who received VOTRIENT in the pivotal mRCC study.

Table 1 Adverse Reactions Occurring in ≥10 % of mRCC Patients who Received VOTRIENT (Study VEG105192)

	VOTRIENT (N = 290)			Placebo (N = 145)		
Reactions	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	52	3	<1	9	<1	0
Nausea	26	<1	0	9	0	0
Vomiting	21	2	<1	8	2	0
Abdominal pain	11	2	0	1	0	0
Vascular disorders						
Hypertension	40	4	0	10	<1	0
General disorders and administrative site conditions						
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Skin and subcutaneous tissue disorders						
Hair colour changes	38	<1	0	3	0	0
Metabolism and nutrition disorders						
Anorexia	22	2	0	10	<1	0
Nervous system disorder						
Headache	10	0	0	5	0	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other notable treatment-emergent adverse reactions in mRCC patients with an incidence <10% (all grades) include:

Blood and lymphatic system disorders: thrombocytopenia (8%), neutropenia (5%), leucopenia (3%), lymphopenia (2%)

Cardiac disorders: myocardial ischaemia* (1%), QT Prolongation* (1%), myocardial infarction/ischemia* (1.7%), Torsade de Pointes* (<1%), cardiac dysfunction* (<1%), myocardial infarction* (<1%)

Endocrine disorders: hypothyroidism* (7%)

Gastrointestinal disorders: dyspepsia (5%), stomatitis (4%), flatulence (3%), gastrointestinal perforations* (<1%), gastrointestinal fistula* (<1%)

General disorders and administration site conditions: chest pain (5%)

Hepatobiliary disorders: hyperbilirubinemia* (4%), abnormal hepatic function* (3%), hepatotoxicity (2%)

Infections and infestations: urinary tract infection (4%)

Investigations: weight decreased (9%)

Metabolism and nutrition disorders: hyperkalemia (3%)

Nervous system disorders: dysguesia (altered taste 8%), paraesthesia (3%), transient ischemic attack* (1.4%), cerebral vascular accident (<1%)

Renal and urinary disorders: proteinuria* (9%), dysuria (2%)

Respiratory, thoracic and mediastinal disorders: epistaxis (2%), dysphonia (4%), pneumothorax* (<1%)

Skin and subcutaneous disorders: alopecia (8%), rash (8%), palmar-plantar erythrodysesthesia (hand-foot syndrome 6%), skin depigmentation (3%), hyperhidrosis (3%)

Vascular disorders: hematuria (4%), epistaxis (2%), hemoptysis* (2%), rectal hemorrhage* (1%), venous thromboembolic events (1%), cerebral haemorrhage* (<1%), pulmonary hemorrhage* (<1%), gastrointestinal hemorrhage* (<1%), genitourinary hemorrhage* (<1%)

*see WARNINGS AND PRECAUTIONS for additional information

Soft Tissue Sarcoma

Table 2 presents the most common adverse reactions occurring in ≥ 10 % of patients who received VOTRIENT in the pivotal STS study.

Table 2 Adverse Reactions Occurring in ≥10% of patients with STS who Received VOTRIENT (study VEG110727)

	VOTRIENT (N = 240)			Placebo (N = 123)		
Adverse Reactions	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**
Fatigue	65	13	<1	48	4	<1
Diarrhea	59	5	0	15	<1	0
Nausea	56	3	0	22	2	0
Weight decreased	48	4	0	15	0	0
Hypertension	42	7	0	6	0	0
Appetite decreased	40	6	0	19	0	0
Hair color changes	39	0	0	2	0	0
Vomiting	33	3	0	11	<1	0
Tumour pain	29	8	0	21	7	2
Dysgeusia	28	0	0	3	0	0
Headache	23	<1	0	8	0	0
Musculoskeletal pain	23	2	0	20	2	0
Myalgia	23	2	0	9	0	0
Gastrointestinal pain	23	3	0	9	4	0
Dyspnea	20	5	<1	17	5	<1
Exfoliative rash	18	<1	0	9	0	0
Cough	17	<1	0	12	<1	0
Peripheral edema	14	2	0	9	2	0
Alopecia	12	0	0	<1	0	0
Dizziness	11	<1	0	4	0	0
Skin disorder[b]	11	2	0	<1	0	0
Skin hypopigmentation	11	0	0	0	0	0
Stomatitis	11	<1	0	3	0	0
Chest pain	10	2	0	6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

[b] 27 of the 28 cases of skin disorder were palmar-plantar erythrodysesthesia.

Other adverse reactions observed with an incidence <10% in STS patients treated with VOTRIENT include:

Blood and lymphatic system disorders: Thrombotic microangiopathy (<1%)

Cardiac disorders: cardiac dysfunction* (11%), myocardial dysfunction* (5%), QT Prolongation* (2%), myocardial infarction/ischemia* (2%)

Endocrine disorders: hypothyroidism* (8%).

Gastrointestinal disorders: dyspepsia (7%), abdominal pain upper (8%), dry mouth (7%), gastrointestinal perforations or fistula* (1%)

General disorders and administration site conditions: insomnia (9%), chills (5%)

Nervous system disorders: dysphonia (8%), vision blurred (5%), cerebral vascular accident (<1%)

Renal and urinary disorders: proteinuria* (1%), nephrotic syndrome (<1%)

Respiratory, thoracic and mediastinal disorders: Pneumothorax (3%)

Skin and subcutaneous disorders: dry skin (6%), nail disorder (5%)

Vascular disorders: pulmonary hemorrhage* (1%), epistaxis (8%), mouth hemorrhage* (3%), anal hemorrhage* (2%), venous thromboembolic events* (5%), gastrointestinal hemorrhage* (<1%), peritoneal hemorrhage (<1%), hematuria (<1%), cerebral hemorrhage* (<1%) including intracranial hemorrhage, subarachnoid hemorrhage

*see WARNINGS AND PRECAUTIONS for additional information

Metastatic Renal Cell Carcinoma and Soft Tissue Sarcoma

Other adverse reactions observed more commonly in mRCC and STS patients treated with VOTRIENT with incidence more than 2% greater than placebo included:

Bradycardia: Based on heart rate measurement (<60 beats per minute), asymptomatic bradycardia was observed in 12% (33/280) patients treated with VOTRIENT and in 8% (11/144) of patients on the placebo arm in the randomized RCC trial. In the randomized trial of VOTRIENT for the treatment of STS, asymptomatic bradycardia was observed in 10% (24/238) of patients treated with VOTRIENT and in 2% (2/121) patients on the placebo arm. Symptomatic bradycardia has been identified rarely (<0.1%) based on a review of the pazopanib clinical trials safety database.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity in both the RCC and STS clinical trials. Patients should be advised how to manage mild diarrhea and instructed to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize this impact.

Amylase/Lipase Elevations: In a single-arm mRCC phase II clinical study, increases in amylase values were observed for 42/184 patients (23%) and increases in lipase values were observed for 48/181 patients (27%). Increased blood amylase as an adverse reaction was reported for 6/225 patients (3%), all were Grade 1 or Grade 2 in severity. Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical mRCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (0.7%).

Pneumothorax: Two of 290 patients treated with VOTRIENT in the mRCC trial developed a pneumothorax. In a clinical trial of VOTRIENT for the treatment of STS, pneumothorax occurred in 8 of 240 patients (3%) treated with VOTRIENT and in no patients in the placebo group. All patients with pneumothorax in the VOTRIENT group had lung metastases at baseline.

Abnormal Hematologic and Clinical Chemistry Findings

Metastatic renal cell carcinoma

Table 3 presents the most common laboratory abnormalities occurring in ≥15% of patients who received VOTRIENT in the pivotal mRCC studies, if they occurred more commonly in the VOTRIENT arm than in the placebo arm.

Table 3 Selected Laboratory Abnormalities in ≥15 % of mRCC Patients who Received VOTRIENT and More Common than in the Placebo Arm

	VOTRIENT (N=290)			Placebo (N=145)		
Parameters	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades * %**	**Grade 3 %**	**Grade 4 %**
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Calcium decreased	33	1	1	26	1	<1
Sodium decreased	31	4	1	24	4	1
Potassium increased	27	4	<1	23	5	0
Creatinine increased	26	0	<1	25	<1	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0
TSH increased	31	N/A	N/A	5	N/A	N/A

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Grades 1-4.

Amylase/Lipase Elevations: In a single-arm mRCC phase II clinical study, increases in amylase values were observed for 42/184 patients (23%) and increases in lipase values were observed for 48/181 patients (27%).

Soft tissue sarcoma

Table 4 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT in the pivotal STS study, if they occurred more commonly in the VOTRIENT arm than in the placebo arm.

Table 4 Selected Laboratory Abnormalities in ≥ 15 % of STS Patients who Received VOTRIENT and More Common than Placebo Arm (study VEG110727)

	VOTRIENT (N = 240)			Placebo (N = 123)		
Parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematological						
Leukopenia	44	1	0	15	0	0
Neutropenia	33	4	0	7	0	0
Thrombocytopenia	36	3	<1	6	0	0
Lymphocytopenia	43	10	0	36	9	2
Anaemia	27	5	2	23	<1	<1
Chemistry						
ALKP increased	32	3	0	23	<1	0
ALT increased	46	8	2	18	2	<1
AST increased	51	5	3	22	2	0
Albumin decreased	34	<1	0	21	0	0
Glucose increased	45	<1	0	35	2	0
Total Bilirubin increased	29	1	0	7	2	0
Sodium decreased	31	4	0	20	3	0
Potassium increased	16	1	0	11	0	0
TSH increased	34	N/A	N/A	2	N/A	N/A

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of VOTRIENT. This includes spontaneous case reports as well as adverse events from ongoing studies, clinical pharmacology studies and exploratory studies in unapproved indications.

Infections and infestations: Infections (with or without neutropenia; see WARNINGS AND PRECAUTIONS)

Blood and lymphatic system disorders: Thrombotic microangiopathy (including TPP and HUS): (see WARNINGS and PRECAUTIONS).

Hepatobiliary disorders: Gamma-glutamyl transpeptidase increased

Musculoskeletal and connective tissue disorders: Arthralgia, muscle spasms

Urogenital Fistula: Cases of urogenital fistulae were seen in a clinical trial of patients with a cancer type for which VOTRIENT is not approved. Most of the patients in this trial had received radiation therapy to the pelvis prior to entering the trial.

Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS): (see WARNINGS AND PRECAUTIONS).

Eye disorders: Retinal detachment/tear

Respiratory thoracic and mediastinal disorders: Interstitial lung disease/pneumonitis (see WARNINGS AND PRECAUTIONS)

DRUG INTERACTIONS

Overview

Pazopanib is a substrate of CYP3A4 and the multidrug efflux pump P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of pazopanib may be influenced by products that affect CYP3A4 and/or PgP. *In vitro* studies suggest that pazopanib is a substrate of breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influenced by products that affect BCRP.

Pazopanib is a potent *in vitro* inhibitor of proteins UDP glucuronsyltransferase 1 family, polypeptide A1 (UGT1A1) and the organic anion transporter polypeptide 1B1 (OATP1B1). Concomitant administration of pazopanib with UGT1A1 substrates (e.g. irinotecan) should be undertaken with caution. It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (eg. rosuvastatin).

Pazopanib is a weak inhibitor of CYP3A4, CYP2D6 and CYP2C8 based on results from clinical pharmacology studies.

Drug-Drug Interactions

Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4, P-gp, BCRP Inhibitors: Pazopanib is a substrate for CYP3A4, P-gp and BCRP. Coadministration of strong CYP3A4 inhibitors may increase pazopanib concentrations and drug toxicity. In a drug interaction study, concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 and P-gp inhibitor, ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a 66% and 45% increase in mean pazopanib $AUC_{(0-24)}$ and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). In addition, more adverse events were observed when pazopanib was administered in combination with ketoconazole than when pazopanib was administered alone, which included cases of severe hypertension with systolic blood pressure of ~200 mmHg. As pazopanib C_{max} and $AUC_{(0-24)}$ increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg, and as the 800 mg once daily dose of pazopanib alone was not included in this study, pharmacokinetic parameter comparisons across studies were made. These comparisons of pazopanib C_{max} (range of means 27.5 to 58.1 μg/ml) and $AUC_{(0-24)}$ (range of means 487 to 1040 μg*h/ml) after administration of pazopanib 800 mg alone from three other studies and after administration of pazopanib 400 mg plus ketoconazole 400 mg (mean C_{max} 59.2 μg/ml, mean $AUC_{(0-24)}$ 1300 μg*h/ml) in this study indicated that, in the presence of a strong CYP3A4 and P-gp inhibitor, a dose reduction to pazopanib 400 mg once daily may result in systemic exposure higher than that observed after administration of 800 mg pazopanib once daily alone. In addition, it should be noted that in a minority (25%) of patients the dose of 400 mg pazopanib once daily in the presence of ketoconazole resulted in systemic exposure greater than the highest systemic exposure observed in the other studies after administration of 800 mg pazopanib once daily alone.

Coadministration of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) with VOTRIENT (pazopanib hydrochloride) should be avoided. If coadministration of a strong CYP3A4 inhibitor with VOTRIENT cannot be avoided, reduce the dose of VOTRIENT to 400 mg. In such cases there should be close attention to adverse drug reactions and the monitoring should begin earlier and frequency should be increased, especially for hypertension, as patients may have exposure greater than that of the 800 mg dose. Further dose reductions may be needed if adverse effects occur during therapy. Doses higher than 400 mg should not be used.

Administration of 1500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, PgP and BCRP, with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean pazopanib $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg pazopanib alone. A Phase II study evaluating 1500 mg of lapatinib + 800 mg pazopanib was terminated early due to concerns over increased toxicity and/or mortality (see WARNINGS AND PRECAUTIONS, General, Combination with other systemic anti-cancer therapies). Coadministration of VOTRIENT with a CYP3A4, PgP or BCRP inhibitor may result in an increase in plasma pazopanib concentrations.

CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations and should be avoided due to the potential for reduced effectiveness of the drug.

Drugs that Inhibit or Induce Transporters

Concomitant treatment with strong inhibitors of P-glycoprotein (P-gp) or inhibitors of both PgP and the breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib (see ***CYP3A4 Inhibitors*** above). Coadministration with inducers of P-gp should be avoided due to the risk of reduced effectiveness of the drug.

Effects of Pazopanib on CYP Substrates

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. Clinical pharmacology studies, using VOTRIENT 800 mg once daily, have demonstrated that VOTRIENT does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. VOTRIENT resulted in an increase of approximately 30% in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Coadministration of VOTRIENT 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively. Coadministration of VOTRIENT with agents with a narrow therapeutic window that are substrates for CYP3A4, CYP2C8 and CYP2D6 should be avoided.

Drugs that Raise Gastric pH

Solubility of pazopanib is pH-dependent and drugs that raise gastric pH may decrease pazopanib absorption. In a drug-drug interaction study, administration of esomeprazole in the evening and VOTRIENT in the morning for 5 days decreased the bioavailability of VOTRIENT by approximately 40% (AUC and C_{max}). Systemic exposures of three pazopanib metabolites were also decreased. The effect of VOTRIENT on esomeprazole (a substrate of CYP2C19 and CYP3A4) exposure was not investigated. Co-administration of VOTRIENT with medicines that increase gastric pH including proton-pump inhibitors, H_2-receptor antagonists and short-acting antacids should be avoided.

Effects of Pazopanib on Transporters

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 µM, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 (e.g. irinotecan) and OATP1B1 (e.g. rosuvastatin).

Effect of concomitant use of VOTRIENT and Simvastatin

Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations. Across monotherapy studies with VOTRIENT, ALT > 3xULN was reported in 126 / 895 (14 %) of patients who did not use statins, compared with 11/41 (27 %) of patients who had concomitant use of simvastatin (p = 0.038). If a patient receiving concomitant therapies develops ALT elevations, follow the recommendations for VOTRIENT dose modifications (see Hepatic in WARNINGS AND PRECAUTIONS) and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT.

Drugs that affect the heart rate

Heart rate lowering drugs: VOTRIENT results in a decrease in heart rate (see WARNINGS AND PRECAUTIONS, Cardiovascular, ACTIONS AND CLINICAL PHARMACOLOGY, Cardiovascular). The concomitant use of VOTRIENT with other heart rate-lowering drugs, such as antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, and sphinosine-1 phosphate receptor modulators should be undertaken with caution.

QTc Prolonging Drugs: The concomitant use of VOTRIENT with QTc-prolonging drugs should be undertaken with caution because decreased heart rate can increase the risk of proarrhythmia in patients receiving these drugs. Drugs that have been associated with QTc interval prolongation and/or Torsade de Pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all class members have been implicated in QT/QTc prolongation and/or Torsade de Pointes.

- Antiarrhythmics (Class IA, e.g., quinidine, procainamide, disopyramide; Class III, e.g. amiodarone, sotalol, ibutilide, dronedarone; Class IC, e.g. flecainide, propafenone)
- Antipsychotics (e.g. chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- Antidepressants (e.g. amitriptyline, imipramine, maproptiline, fluoxetine, citalopram, venlafaxine)
- Opioids (e.g.methadone)
- Macrolide antibiotics (e.g. erythromycin, clarithromycin, telithromycin)
- Quinolone antibiotics (e.g. moxifloxacin, levofloxacin, ciprofloxacin)
- Antimalarials (e.g. quinine)
- Azole antifungals (e.g. ketoconazole, fluconazole, voriconazole)
- Gastrointestinal drugs (e.g. domperidone, 5HT3 antagonists such as granisetron, ondansetron, dolasetron)
- Beta 2-adrenoreceptor agonists (e.g. salmeterol, formoterol)

- Other tyrosine kinase inhibitors (e.g, sunitinib, nilotinib, lapatinib, sorafenib)
- Histone Deacetylase Inhibitors (e.g, vorinostat)
- Tacrolimus

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly-approved drugs that prolong the QT/QTc interval, as well as for older drugs for which these effects have recently been established.

Drug-Food Interactions

Grapefruit, grapefruit juice and other foods that are known to affect CYP3A4 and PgP activity should be avoided during treatment.

Administration of VOTRIENT with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, VOTRIENT should be administered at least 1 hour before or 2 hours after a meal.

Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4 that may increase the metabolism of pazopanib and decrease pazopanib blood levels.

Drug-Laboratory Interactions

Interactions between VOTRIENT and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

The recommended dose of VOTRIENT for the treatment of mRCC and STS is 800 mg orally once daily.

VOTRIENT should be taken without food (at least one hour before or two hours after a meal) (see ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics).

Dosing Considerations

Dose modification, either an increase or decrease in dose, should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of VOTRIENT should not exceed 800 mg.

Hepatic Impairment: VOTRIENT is not recommended in patients with baseline plasma bilirubin concentrations >1.5 X ULN (with direct bilirubin >35%) and ALT elevations >2 X ULN, or who have moderate or severe hepatic impairment (Child-Pugh B and C). No

formal studies have been carried out in patients with mild hepatic impairment and caution is recommended in these patients (see ACTION AND CLINICAL PHARMACOLOGY; Special Populations and Conditions).

Renal Impairment: No dose adjustments are recommended for patients with mild or moderate renal impairment. Patients with > 1 g protein (24 h collection) at baseline were excluded from the pivotal clinical studies. VOTRIENT is not recommended for patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY; Special Populations and Conditions).

Coadministration with strong CYP3A4 inhibitor: If coadministration of a strong CYP3A4 inhibitor with VOTRIENT cannot be avoided, reduce the dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy. Doses higher than 400 mg should not be used (see DRUG INTERACTIONS; Drug-Drug Interactions; CYP3A4 Inhibitors).

Geriatrics: No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.

Missed Dose

If a dose is missed, VOTRIENT should not be taken if it is less than 12 hours until the next dose.

Administration

For oral use.

VOTRIENT should be taken whole with a glass of water and must not be broken or crushed (see ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Pazopanib doses up to 2000 mg have been evaluated in clinical trials. Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2000 mg and 1000 mg daily, respectively.

Treatment of overdoses with VOTRIENT should consist of general supportive measures. There is no specific antidote for overdosage of VOTRIENT.

Hemodialysis is not expected to enhance the elimination of VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pazopanib is an orally administered, small molecule, multi-target tyrosine kinase inhibitor (TKI). It is a potent inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR –β receptors in cells. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumour xenografts in mice.

Pharmacokinetics

Table 5 Pazopanib Pharmacokinetic Parameters After Administration of 800 mg Pazopanib Once Daily for 17 Days (N=18)

	AUC(0-24) (μg*h/mL)	**Cmax** (μg/mL)	**tmax**[1] (h)
Geometric mean	1,037	58.1	3.13
CVb%	34.3	33.3	1.0-8.0

[1] tmax reported as median and range

Results from a population pharmacokinetic analysis suggest that the coefficients of variation for inter-subject variability in pazopanib oral clearance and volume of distribution were 52.3% and 67.1%, respectively.

Absorption: Pazopanib is absorbed orally with median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. Bioavailability differences accounts for non-linear kinetics between 200 to 800 mg (400 mg is approximately 1.4 X more bioavailable than 800 mg). No consistent increases in AUC and C_{max} were observed when the oral dose was increased above 800 mg (plateau was reached). The oral bioavailability of pazopanib reflects absorption that is limited by solubility and reaches saturation at doses above 800 mg once daily.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, pazopanib should be administered at least 1 hour before or 2 hours after a meal (see DOSAGE AND ADMINISTRATION).

Administration of a single pazopanib 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46% and C_{max} by approximately 2 fold and decreased t_{max} by approximately 1.5 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets should not be crushed (see DOSAGE AND ADMINISTRATION).

Distribution: Binding of pazopanib to human plasma protein in vivo was greater than 99% with no concentration dependence over the range of 10-100 μg/ml. *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (PgP) and breast cancer resistant protein (BCRP).

Metabolism: Results from *in vitro* studies demonstrated that the metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

Excretion: Pazopanib is eliminated slowly with mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Most of the oral dose (60-70%) is not metabolized and excreted unmodified in the feces. Approximately 7-15% of the administered dose is recovered as metabolites in the feces, with renal elimination accounting for <4% of the administered dose.

Special Populations and Conditions

Hepatic Insufficiency: The safety and pharmacokinetics of VOTRIENT in patients with pre-existing hepatic impairment have not been fully established (see WARNINGS AND PRECAUTIONS). Pharmacokinetic data from patients with normal hepatic function (n = 12) and moderate (n = 7) hepatic impairment indicate that pazopanib clearance was decreased by approximately 50 % in those with moderate hepatic impairment [total bilirubin > 1.5 to 3 X Upper Limit of Normal (ULN)]. However, patients with moderate hepatic impairment experienced dose-limiting toxicity at the 400 mg dose. There are no data in patients with severe hepatic impairment (total bilirubin > 3 X ULN). There are no

data to support dosing recommendation in patients with mild hepatic impairment (see WARNINGS AND PRECAUTIONS).

Renal Insufficiency: Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance ≥30mL/min) were included in clinical studies for VOTRIENT.

Renal impairment is not expected to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see *Pharmacokinetics - Excretion*). In a population pharmacokinetic analysis using 408 patients with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary. There is no experience of VOTRIENT in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis; therefore, use of VOTRIENT is not recommended in these patients.

Pharmacodynamics

Cardiovascular: A randomised, double-blind, placebo-controlled, parallel group, repeat dose study was performed to evaluate the effect of VOTRIENT on electrocardiographic parameters in patients with solid tumours. Evaluable patients received placebo (n=32) or VOTRIENT (n=33) administered as a dose of 800 mg for 7 days, then as a 1600 mg dose with food on the eighth day. This achieved plasma levels that were approximately 1.3 to 1.4 times higher than those associated with the recommended 800 mg once daily dose. Serial ECG data were collected for 8 h post-dosing on day 8. VOTRIENT caused a decrease in heart rate at all time points on days 8 that reached mean -14.5 (90% CI -17.8, -11.2) bpm at 8 h (the last time point tested).

The PR interval was significantly increased at 6 and 8 h post-dosing, reaching a mean difference versus placebo of 7.26 (90% CI 2.64, 11.88) ms at 8 h post-dosing.

VOTRIENT was associated with statistically significant increases in systolic and diastolic blood pressure on day 8 of treatment. The maximum observed difference versus placebo in systolic blood pressure was mean 16.48 (90% CI 11.04, 21.93) mmHg at 8 h post-dosing, whilst the maximum observed difference versus placebo in diastolic blood pressure was mean 11.83 (90% CI 9.11, 14.54) mmHg, also at 8 h. Antihypertensive medications were used by 41% of patients in this trial.

STORAGE AND STABILITY

Store between 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The 200 mg tablets of VOTRIENT (pazopanib as pazopanib hydrochloride) are modified capsule shaped, grey, film coated with GS JT debossed on one side and are available in bottles of 120 tablets.

The 400 mg* tablets of VOTRIENT are modified capsule shaped, yellow, film coated with GS UHL debossed on one side and are available in bottles of 30 tablets and 60 tablets.

The tablet core contains the following excipients; magnesium stearate, microcrystalline cellulose, povidone (K30) and sodium starch glycollate. The tablet coating contains the following excipients; hypromellose, iron oxide black (E172 – 200mg tablet), iron oxide yellow (E172 – 400mg tablet), macrogol, polysorbate 80 and titanium dioxide (E171).

*VOTRIENT 400 mg tablets not available in Canada.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

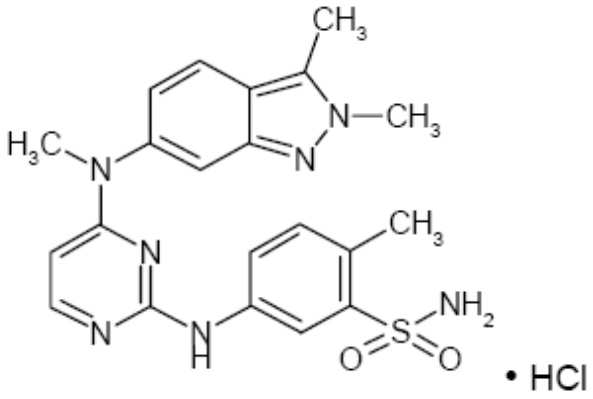
Common name: pazopanib hydrochloride

Chemical name: 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide monohydrochloride

Molecular formula: $C_{21}H_{23}N_7O_2S$•HCl

Molecular mass: 473.99 g/mol (437.53 g/mol free base)

Structural formula:



Physicochemical properties: Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

CLINICAL TRIALS

Metastatic Renal Cell Carcinoma

The safety and efficacy of VOTRIENT (pazopanib hydrochloride) in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled phase III multi-centre study.

The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the principle secondary endpoint is overall survival (OS). The other objectives were to evaluate the overall response rate, duration of response and quality of life measures.

Trial Design

Patients with metastatic RCC (mRCC) were randomized (2:1) to receive VOTRIENT 800 mg once daily, or placebo with best supportive care, following stratification by ECOG performance status (0 vs. 1); prior nephrectomy (yes vs. no); and prior therapy (no prior systemic therapy vs. one prior cytokine-based therapy).

Disease assessments were performed every 6 weeks until Week 24, and every 8 weeks thereafter until disease progression. Tumour lesion selection, classification and tumour response evaluation were performed using RECIST. All imaging scans were evaluated by an independent review committee (IRC) of radiologists.

After documented radiological progression, patients could be unblinded by the investigator; those randomised to placebo were then able to receive open-label VOTRIENT 800 mg/day.

Study Demographics and Baseline Characteristics

Table 6 below summarizes the patient demographics in the VOTRIENT pivotal clinical trial.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 were second line patients who received one prior IL-2 or INF-based therapy. The performance status (ECOG) was similar between the VOTRIENT and placebo groups (ECOG 0: 42% vs. 41%, ECOG 1: 58% vs. 59%). All patients had metastatic disease at screening with either clear cell histology or predominantly clear cell histology. Approximately half of all patients had 3 or more organs involved in their disease and most patients had the lung (74%), and/or lymph nodes (54%) as a metastatic location for disease at baseline.

A similar proportion of patients in each arm were treatment-naïve and cytokine-pre-treated (53% and 47% in VOTRIENT arm, 54% and 46% in placebo arm). In the cytokine-pre-treated subgroup, the majority (75%) had received interferon based treatment.

Similar proportions of patients in each arm had prior nephrectomy (89% and 88% in the VOTRIENT and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the VOTRIENT and placebo arms, respectively.

Table 6 Summary of patient demographics in pivotal clinical trial of VOTRIENT in mRCC (ITT Population), (VEG105192)

Characteristics	**VOTRIENT N=290**	**Placebo N=145**	**Total N=435**
Age, Years			
Median (range)	59 (28-85)	60 (25-81)	59 (25-85)
Gender, %			
Female	32	25	29
Male	68	75	71
Age Group, %			
<65 years	68	59	65
≥65 years	32	41	35
Race, %			
White	87	84	86
Asian	12	16	14
Black	<1	0	<1
Other	<1	0	<1
Performance Status, %			
ECOG 0	42	41	42
ECOG 1	58	59	58
Prior Treatment, %			
Treatment naïve	53	54	54
Cytokine-pre-treated	47	46	47

Study results

The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (treatment-naïve and cytokine pre-treated). OS data were not mature at the time of the final PFS analysis.

A clinically and statistically significant improvement in PFS was observed in the VOTRIENT treated arm compared to the placebo-treated arm with a hazard ratio of 0.46 (95% CI, 0.34, 0.62, p<0.0000001), indicating a 54% reduction in risk of progression or death with more than doubling of the median PFS (9.2 vs. 4.2 months).

Overall efficacy results by independent review committee are presented in Table 7.

Table 7 Overall Efficacy Results in mRCC by Independent Review Committee (VEG105192)

Endpoints/ Study population	VOTRIENT	Placebo	HR (95% CI)	P value (two-sided)
PFS	**Median (months)**			
Overall* (ITT)	N=290	N=145		
	9.2	4.2	0.46 (0.34, 0.62)	<0.0000001
Treatment-naïve	N=155	N=78		
	11.1	2.8	0.40 (0.27, 0.60)[a]	<0.0000001
Cytokine pre-treated	N=135	N=67		
	7.4	4.2	0.54 (0.35, 0.84)[a]	<0.001
Response rate	**% (95% CI)**			
Overall	N=290	N=145		
	30 (25.1 ,35.6)	3 (0.5, 6.4)	-	<0.001

* Treatment naïve and cytokine pre-treated populations; CI: confidence interval; PFS: progression free survival; ITT: intent-to-treat.
a. Unadjusted estimate.

No significant treatment-related difference in interim overall survival was noted.

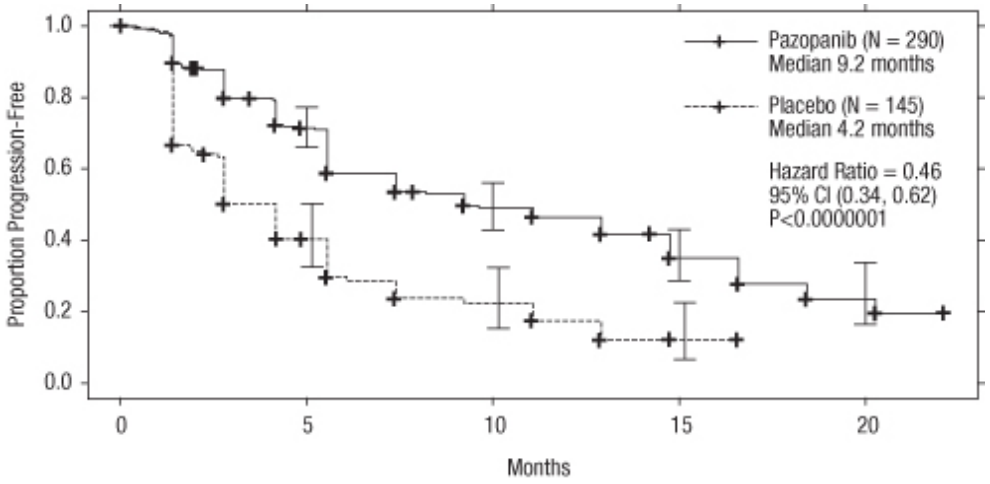
The Response Rate (RR), defined as the percentage of patients who achieved either a confirmed complete response or partial response according to RECIST criteria, was significantly higher in the VOTRIENT arm compared with the placebo arm. By independent review, the difference in RR was 26.9% (95% CI: 20.8, 33.0, p<0.001) and by investigator review was 29.3% (95% CI: 22.5, 36.1, p<0.001). The independent- and investigator-evaluated best confirmed responses by RECIST were similar for both treatment arms.

For patients who responded to treatment, the median duration of response was 58.7 weeks as per independent review.

The median overall survival (OS) data at the protocol specified final survival analysis were 22.9 months and 20.5 months [HR = 0.91 (95 % CI: 0.71, 1.16; p = 0.224)] for patients randomized to the VOTRIENT and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received VOTRIENT in the extension part of this study following disease progression. Sixty-six percent of placebo patients received post-study therapy compared to 30 % of VOTRIENT patients.

Kaplan-Meier curves for progression-free survival by Independent Review Committee assessment for the overall (ITT) population are presented in Figure 1.

Figure 1 **Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall mRCC Population (Treatment-Naïve and Cytokine Pre-Treated Populations); (VEG105192)**



Additional subgroup analysis demonstrated that the treatment effect of VOTRIENT on PFS in all subgroups analyzed, including analysis by treatment-naïve population (Table 7), cytokine pre-treated population (Table 7), gender, age, ECOG PS, and the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic risk category, was consistent with the primary analysis.

In the pivotal study, the QoL assessments were based on blinded self-reported global scores from two protocol-specified questionnaires, EORTC QLQ-C30 and EuroQoL EQ-5D. Analysis was based on patients who continued on therapy in both arms, prior to progression. The assessments showed no difference between treatment with VOTRIENT or placebo ($p>0.05$).

Soft Tissue Sarcoma

The safety and efficacy of VOTRIENT in STS were evaluated in a randomized, double-blind, placebo-controlled multi-centre study (VEG110727).

The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS), based on the ITT population, and the principle secondary endpoint was overall survival (OS).

Trial Design

Adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who had received prior chemotherapy for metastatic disease or who had progressed within 12 months after (neo)adjuvant therapy were eligible to enter the trial. Patients were required to have disease progression on or after, or be intolerant to, an anthracycline-based regimen. Patients who have been previously treated with inhibitors of angiogenesis

and/or VEGF or VEGFR-targeting agents were excluded. Prior to study enrollment, all patients had to have confirmed disease progression.

The following tumour types were eligible: Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumours), so-called fibrohistiocytic [pleomorphic malignant fibrous histiocytoma (MFH), giant cell MFH, inflammatory MFH], leiomyosarcoma, malignant glomus tumours, skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma; excluding chondrosarcoma, Ewing tumours / primitive neuroectodermal tumours), malignant peripheral nerve sheath tumours, undifferentiated soft tissue sarcomas not otherwise specified (NOS) and other types of sarcoma (not listed as ineligible).

The following tumour types were not eligible: Adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumours/ primitive neuroectodermal tumours, GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.

Patients with adipocytic sarcoma were excluded because activity (PFS at week12) observed with VOTRIENT in a phase II study (VEG20002) in these tumours was indeterminant.

Prior to randomization, eligible subjects were stratified by the factors of WHO performance status (WHO PS) (0 or 1) at baseline and the number of lines of prior systemic therapy for advanced disease (0 or 1 vs. 2+). Patients were randomized (2:1) to receive VOTRIENT 800 mg once daily or placebo.

Treatment activity was assessed at 4 week intervals during the first 12 weeks of treatment and every 8 weeks thereafter until progression or the start of a new anti-cancer therapy; objective response and progression were defined according to the RECIST v1.0. Blinded independent radiological review was used for the primary analysis. Each patient was to be followed until death or withdrawal of consent.

Study demographics and baseline characteristics

A total of 369 patients were randomized in the study and formed the ITT population.

Table 8 below summarizes the patient demographics and baseline characteristics in the VOTRIENT STS pivotal clinical trial.

Table 8 Summary of patient demographics and characteristics in pivotal clinical trial of VOTRIENT in STS: ITT Population (study VEG110727)

Characteristics	VOTRIENT N=246	Placebo N=123	Total N=369
Age, Years			
Median (range)	56.0 (18,78)	51.0 (20,83)	55 (18,83)
Gender, n (%)			
Female	147 (60)	69 (56)	216 (59)
Male	99 (40)	54 (44)	153 (41)
Race, %			
White	71	74	72
Asian	23	22	22
Other	6	4	6
STS Tumour Subtype, n (%)			
Leiomyosarcoma	109(44)	49(40)	158(43)
Synovial sarcoma	25(10)	13(11)	38(10)
Other STS*	112(46)	61(49)	173(47)
Tumour Grade**, n (%)			
Low (grade 1)	33 (13)	11 (9)	44(12)
Intermediate (grade 2)	70 (28)	29 (24)	99(27)
High (grade 3)	72 (29)	44 (36)	116(31)
Performance Status, n (%)			
WHO PS 0	118(48)	60(49)	178(48)
WHO PS 1	128(52)	63(51)	191(52)
Prior Systemic Treatment for Advanced Disease, n(%)			
0 lines	14(6)	13(11)	27(7)
1 lines	96(39)	39(32)	135(37)
2 lines	85(35)	44(36)	129(35)
3 lines	35(14)	18(15)	53(14)
4 lines	16(7)	9(7)	25(7)
Prior Adjuvant Therapy	43 (17)	26 (21)	69 (19)
Prior Neoadjuvant Therapy	31 (13)	19 (15)	50 (14)
Prior Maintenance Therapy	10 (4)	4 (3)	14 (4)
Prior Chemotherapy	246 (100)	123 (100)	369 (100)
Doxorubicin	242 (98)	121 (98)	363 (98)
Ifosfamide	164 (67)	93 (76)	257 (70)
Docetaxel	69 (28)	35 (28)	104 (28)
Gemcitabine	85 (35)	42 (34)	127 (34)
Trabectedin	38 (15)	22 (18)	60 (16)
mTOR inibitors	11 (4)	3 (2)	14 (4)
Other	105 (43)	53 (43)	158 (43)

* "Other STS" included fibroblastic type (N=32), so-called fibrohistiocytic tumours (N=32), tumours of uncertain differentiation (N=33), undifferentiated sarcomas NOS (N=20), MPNST (N=12), vascular tumours (N=7), skeletal muscle/rhabdomyosarcoma (N=2), adipocytic tumours (N=1), pericytic tumours (N=1), chondro-osseous tumours (N=1) and "other" tumour types (N=32) of sarcomas not listed as ineligible.

**In patients with central pathology grading.

Study Results

The initial analysis of the primary endpoint PFS was based on disease assessment by independent radiological review in the entire ITT study population.

The median duration of follow-up of patients (defined as date of randomization to date of last contact or death) was similar for both treatment arms [9.36 months for placebo (range 0.69 to 23.0 months) and 10.04 months for VOTRIENT (range 0.2 to 24.3 months)].

A clinically and statistically significant improvement in PFS was observed in the VOTRIENT treated arm compared to placebo-treated arm, with a hazard ratio of 0.35 (95% CI, 0.26, 0.48, $p < 0.001$), indicating a 65% reduction in risk of progression or death, more than doubling the median PFS (20.0 vs 7.0 weeks).

Disease assessment occurred at 4 week intervals through week 12 and at 8 week intervals thereafter. Since the VOTRIENT median PFS was 20 weeks it is possible that if a disease assessment had been done at 16 weeks the median PFS would have been earlier.

Overall efficacy results as independently assessed are presented in Table 9.

Table 9 Overall efficacy results in STS by independent assessment (study VEG110727)

	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
Overall ITT Population	N=246	N=123		
PFS				
Overall ITT population Median PFS (weeks)	20.0	7.0	0.35 (0.26, 0.48)	< 0.001
Leiomyosarcoma Median PFS (weeks)	N = 109 20.1	N = 49 8.1	0.37 (0.23, 0.60)	< 0.001
Synovial sarcoma Median PFS (weeks)	N = 25 17.9	N = 13 4.1	0.43 (0.19, 0.98)	0.005
'Other' STS Median PFS (weeks)	N = 112 20.1	N = 61 4.3	0.39 (0.25, 0.60)	< 0.001
Overall survival (OS)*				
Overall ITT population Median OS (months)	12.6	10.7	0.87 (0.67, 1.12)	p=0.256
Leiomyosarcoma Median OS (months)	N=109 16.7	N=49 14.1	0.84 (0.56, 1.26)	p=0.363
Synovial sarcoma Median OS (months)	N=25 8.7	N=13 21.6	1.62 (0.79, 3.33)	p=0.115
'Other' STS Median OS (months)	N=112 10.3	N=61 9.5	0.84 (0.59, 1.21)	p=0.325
Response Rate (CR + PR) % (95 % CI)	4 (2.3, 7.9)	0 (0.0, 3.0)	-	-
Duration of response Median (weeks) (95 % CI))	38.9 (16.7, 40.0)	-	-	- -

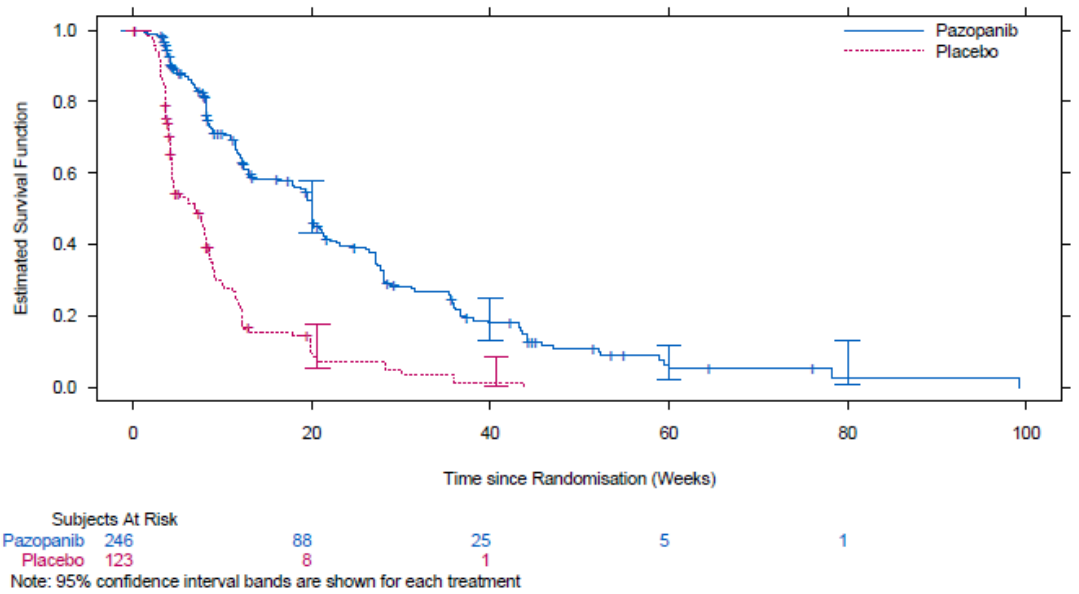
HR = Hazard ratio; ITT = Intent to treat; PFS = Progression-free survival; CR = Complete Response; PR = Partial Response; NS = not significant.

* Overall survival for the respective STS histological subgroups (leiomyosarcoma, synovial sarcoma and "Other" STS) should be interpreted with caution due to the small number of subjects and wide confidence intervals

Similar to the assessments by independent radiology review, a clinically meaningful and statistically significant improvement in PFS based on investigator assessments was observed in the VOTRIENT arm compared with the placebo arm (HR: 0.39; 95 % CI, 0.30 to 0.52, p <0.001).

A greater percentage of patients on the placebo arm (69%) than the VOTRIENT arm (53%) received systemic anti-cancer therapy (chemotherapy and/or targeted therapy) excluding surgery and radiotherapy post discontinuation of study drug.

Figure 2 **Kaplan-Meier Curve for Progression-Free Survival in STS by Independent Assessment for the Overall Population (VEG110727)**



No significant difference in OS was observed between the two treatment arms at the final OS analysis performed after 76% (280/369) of the events had occurred. At the protocol-specified final analysis of OS, the median OS was 12.6 months for patients randomized to VOTRIENT and 10.7 months for the placebo arm [HR = 0.87 (95% CI:0.67, 1.12)].

DETAILED PHARMACOLOGY

Refer to PART I, ACTION AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with pazopanib have not been performed, mice given 1000 mg/kg/day (approximately 1.5 times the human clinical exposure based on AUC) for 13 weeks had proliferative lesions noted in the liver including eosinophilic foci in 2 females and a single case of adenoma in another female.

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat *in vivo* micronucleus assay).

In female rats, reduced fertility was present at 300 mg/kg (approximately 0.8 times the human clinical exposure based on AUC). Increased pre- and post-implantation loss and early resorptions were noted at dosages ≥10mg/kg/day (approximately 0.2 times the human clinical exposure based on AUC). Decreased corpora lutea were observed in monkeys given 500 mg/kg/day for up to 34 weeks, in mice given ≥300 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given 300 mg/kg/day for 26 weeks (approximately equal to, 0.6, 1.4 and 0.9 times the human clinical exposure based on AUC, respectively).

Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at ≥100 mg/kg/day (approximately 0.5 times the human clinical exposure based on AUC) following 15 weeks of dosing. Following 26 weeks of dosing, there were decreased testicular and epididymal weights, atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis of male rats given doses ≥30 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC).

Pazopanib produced foetal teratogenic effects (including cardiovascular malformations and delayed ossification), reduced foetal body weight, and embryo lethality in rats at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC). In rabbits, maternal toxicity (body weight loss, reduced food consumption, and abortion) were observed at doses ≥30 mg/kg/day (approximately 0.007 times the human clinical exposure based on AUC), while foetal weight was reduced at doses ≥3 mg/kg/day (see WARNINGS AND PRECAUTIONS; Special Populations).

Animal Toxicology and/or Pharmacology

In toxicology studies in rats, there were effects in a variety of tissues (bone, teeth, bone marrow, nail beds, reproductive organs, hematological tissues, kidney, adrenal glands, lymph node, pituitary, and pancreas) consistent with VEGFR inhibition and/or disruption of VEGF signalling pathways with some effects occurring at doses of 3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC).

In repeat-dose toxicology studies in rats including 4-week, 13-week and 26-week administration, toxicities in bone, teeth and nail beds were observed at doses ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13- and 26-week studies with rats. Body weight loss and morbidity were observed at these doses. Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in rats at ≥30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks (see PART I, INDICATIONS and CLINICAL USE, Pediatrics).

Hepatic effects included mild elevations of liver transaminases in rodents and bilirubin elevations in monkeys without associated histopathology at doses that produced systemic exposures approximately 0.1 and 0.6 times the human clinical exposure, respectively. Vascular pathology was observed in intrahepatic branches of the hepatic artery and arterioles near the liver hilus in rats administered 500mg/kg/day for 8 days.

To determine the tolerability and toxicokinetics of pazopanib in juvenile rats a dose-ranging study was conducted. Pazopanib was administered from Day 9 through Day 35 post-partum (pp) at 0.3, 3, 30, 300 and 1000 mg/kg/day and from Day 21 through Day 35 pp at 30, 300 and 1000 mg/kg/day. Differences in tolerability were noted. Specifically, when dosing began on Day 21 pp (which approximates a human paediatric age of 2 years), dose levels up to 1000 mg/kg (up to 0.84x the clinical exposure based on AUC in adults) were tolerated. The only finding consisted of marked decreases in body weight gain from 300 mg/kg. In contrast, when dosing was initiated on Day 9 pp, dose levels ≥ 30 mg/kg (up to 0.4x the clinical exposure based on AUC in adults) were not tolerated due to deaths starting on Day 13 pp. At 300 and 1000 mg/kg, all animals were euthanized or found dead after the first week of dosing. Dose levels of 0.3 and 3 mg/kg (less than 0.01x and 0.1x the clinical exposure based on AUC in adults) were well tolerated from Day 9 pp until Day 35 pp.

To explore the noted difference in sensitivity, an investigative study was conducted wherein juvenile rats aged 9 to 14 days post-partum were dosed at 10 and 100 mg/kg/day (equal to approximately 0.16x and 0.43x human clinical exposure based on AUC in adults, respectively). A dose level of 10 mg/kg was tolerated but resulted in a 60-70% decrease in body weight gain. At 100 mg/kg, deaths and a lack of body weight gain was observed. At both doses, profound effects on organ growth and maturation were observed and included decreased absolute kidney weight (up to -35% and -48% at 10 and 100 mg/kg, respectively), liver weight (up to -39% and -54% at 10 and 100 mg/kg, respectively), heart weight (up to -43% and -53% at 10 and 100 mg/kg, respectively), brain weight (up to -15% and -21% at 10 and 100 mg/kg, respectively) and lung weight (up to -36% and -49% at 10 and 100 mg/kg, respectively). At 100 mg/kg decreased cell proliferation and increased cell apoptosis was also observed in various organs. Histologically, glomerulopathy was noted at both dose levels with renal endothelial cells being a primary target. Degenerative changes occurred as early as 24 hours after the first dose which progressed to necrosis and loss of endothelium, thinning of glomerular basement membranes, and subsequent effects on mesangial cells and podocytes. These findings suggest that pazopanib interferes with VEGF-dependent glomerular maturation as well as organ growth and development of kidney, heart, liver, and lung in pre-weanling juvenile rats.

A third juvenile toxicity study was conducted to determine the potential effects of pazopanib on viability, growth and development when administered to juvenile rats from Day 21 to 62 pp at 10, 30 and 300 mg/kg/day (less than 1.0x human clinical exposure based on AUC in adults). Two female rats were terminated early due to excessive body weight loss and rats were administered 100 mg/kg for the remainder of the study. In contrast with juvenile animals dosed with pazopanib from Day 9 to Day 21 pp, administration of pazopanib from Day 21 to Day 62 pp was associated with toxicological

findings that were similar to those noted in adult rats and include decreased body weight gain (≥10 mg/kg), broken and/or loose incisor teeth (≥30 mg/kg), alterations in the femur and tibia (growth plate hypertrophy, thinning of cortical bone, partial physeal closure and tibial fracture at ≥30 mg/kg). Dose-dependent decreases in femoral length occurred at all dose levels and were proportional with body weight effects, suggesting an effect on overall growth of the juvenile animals. Other affected tissues include the trachea, adrenal, pancreas, stomach, duodenum, lymph node, male mammary gland and reproductive organs.

SAFETY PHARMACOLOGY

In safety pharmacology studies, there were no pazopanib-related central and peripheral nervous system, respiratory or cardiovascular effects in rats or monkeys given single oral doses of up to 300 mg/kg or 500 mg/kg, respectively.

A single intravenous dose of 3.75 mg/kg to conscious male cynomolgus monkeys produced a mild, reversible decrease in heart rate (11 to 45 beats/min or 7 to 26%), but had no effect on arterial pressures or body temperature, did not produce any abnormal changes in ECG intervals and there was no evidence of drug-related ECG waveform abnormalities or arrhythmias. The C_{max} and AUC (55µg/mL and 41µg.h/mL, respectively) in this study were within the C_{max} and AUC range seen in the oral cardiovascular study.

In a hERG assay, pazopanib was tested at concentrations of up to 4.137 µM. When the current was expressed as % control and compared to vehicle, there was a very mild effect on hERG tail current but inhibition was not of sufficient magnitude to allow estimation of the IC_{25}, IC_{50} or IC_{75} values.

There were also no treatment-related effects on action potential duration or other action potential parameters when dog Purkinje fibers were incubated with up to 80 nM pazopanib (concentration limited by compound solubility).

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PART III: CONSUMER INFORMATION

PrVOTRIENT®
Pazopanib Tablets

This leaflet is part III of a three-part "Product Monograph" published when VOTRIENT was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VOTRIENT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

VOTRIENT is used in the treatment of:

Metastatic kidney cancer (when cancer cells have spread from the kidney to other parts of the body).

Selective subtypes of advanced soft tissue sarcoma in patients who have received prior chemotherapy. Soft tissue sarcoma is a type of cancer that occurs in muscles, blood vessels or other tissues that support, surround and protect the organs.

VOTRIENT is shown to slow tumour growth, however, it is not known whether VOTRIENT prolongs overall survival or improves the quality of life of patients.

What it does:

VOTRIENT prevents the activity of a special group of proteins which are known to be involved in the growth and spread of cancer cells.

When it should not be used:

VOTRIENT must not be used if you are allergic to pazopanib hydrochloride, or any of the other ingredients in VOTRIENT (see What the important nonmedicinal ingredients are).

VOTRIENT must not be used in children under two years of age.

What the medicinal ingredient is:

The active ingredient is pazopanib hydrochloride.

What the important nonmedicinal ingredients are:

The other ingredients are hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, povidone (K30), polysorbate 80, sodium starch glycollate, titanium dioxide (E171), iron oxide black (E172) and iron oxide yellow (E172).

What dosage forms it comes in:

VOTRIENT` is available as tablets. Each film coated tablet contains either 200 mg or *400 mg of pazopanib hydrochloride. The 200 mg tablets of VOTRIENT are modified capsule shaped, grey, film coated with GS JT debossed on one side and are available in bottles of 120 tablets.

The *400 mg tablets are modified capsule shaped, yellow, film coated with GS UHL debossed on one side and are available in bottles of 30 tablets or 60 tablets.

*VOTRIENT 400 mg tablets not available in Canada

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

VOTRIENT should be prescribed and managed by a doctor experienced in the use of cancer drugs.

VOTRIENT is not recommended for patients with moderate or severe liver impairment (reduced function).

Serious side effects with the use of VOTRIENT may include the following:

- Liver toxicity
- High blood pressure
- Effect on the electrical activity of the heart (QT/QTc prolongation)
- Heart becomes less effective at pumping blood (cardiac dysfunction)
- Blood clots (arterial thromboembolic or venous thrombotic events and thrombotic microangiopathy)
- Bleeding
- Gastrointestinal perforation (a hole that develops through the wall of the stomach, small intestine or large bowel) and fistula (an abnormal connection between parts of the digestive tract)
- Reversible swelling in the rear part of the brain that can be associated with high blood pressure and can lead to headache, loss of speech or vision, abnormal drowsiness, confusion and/or seizure (Posterior Reversible Encephalopathy Syndrome or Reversible Posterior Leukoencephalopathy Syndrome)

Safety and efficacy of VOTRIENT have not been established in children less than 18 years of age. VOTRIENT must not be used in children under two years of age.

BEFORE you use VOTRIENT talk to your doctor or pharmacist:

- If you have or had heart disease, heart failure or heart attack
- If you have or have had a heart rhythm disorder such as irregular heartbeat, prolongation of the QT interval or any risk factors for Torsade de Pointes (dangerous rapid fluttering of the heart) such as diabetes, low potassium, magnesium or calcium levels, or a history of low heart rate, fainting, or loss of consciousness
- If you have high blood pressure
- If you have liver disease
- If you have problems with bleeding
- If you have gastrointestinal problems
- If you have or had a blood clot in a vein or in a lung
- If you have had prior collapse of a lung
- If you have a kidney problem
- If you have thyroid problems
- If you are going to have a surgical or dental procedure, or if you have had either recently

While you are taking VOTRIENT your doctor will take blood samples to check for any liver problems. You should report any signs or symptoms of liver injury including jaundice (yellowing of whites of eyes or skin), unusual darkening of the urine, anorexia (loss of appetite), nausea, fatigue, right upper abdominal discomfort and vomiting. Your doctor will also take urine samples to check for any kidney problems. You will also have your blood pressure checked. Your doctor will periodically record your electrocardiogram (ECG) to check your heart's electrical conduction.

Your doctor will also check on any recent surgical or dental procedures to see if you are healing properly.

Use a reliable method of contraception to avoid becoming pregnant while you're taking VOTRIENT. If you are pregnant or think you could be, talk to your doctor about the risks and benefits to you and your baby while taking VOTRIENT. Your doctor may recommend that you don't take VOTRIENT while you are pregnant.

Breastfeeding is not recommended during treatment with VOTRIENT. Ask your doctor for advice.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking, or have recently taken any other medicines including any medicines you bought without a prescription. This includes herbal medicines.

Some medicines may affect the way VOTRIENT works or VOTRIENT may affect how other medicines work. These include:

- clarithromycin, ketoconazole, itraconazole, telithromycin, voriconazole (used to treat infections)
- atazanavir, indinavir, nelfinavir, ritonavir, saquinavir (used to treat HIV)
- dextromethorphan (used in cough medicines)
- simvastatin and possibly other statins (used to treat high cholesterol levels)
- medicines that reduce stomach acid (e.g. esomeprazole, ranitidine, magnesium hydroxide)

Also, the following list includes some, but not all, of the drugs that may interact with VOTRIENT to affect the electrical activity of your heart:

- Antiarrhythmics (drugs that stabilize the heart rhythm function, such as quinidine, procainamide, amiodarone, sotalol, etc.)
- Antidepressants (mood disorder drugs)
- Antipsychotics (drugs used to stabilize thinking and behaviour)
- Opioids (e.g. methadone)
- Macrolide antibiotics (such as erythromycin, clarithromycin)
- Fluoroquinolone antibiotics (such as moxifloxacin, levofloxacin, ciprofloxacin)
- Antifungals (such as fluconazole, voriconazole)
- Antimalarials (e.g. quinine)
- Antinauseants e.g. granisetron, ondansetron, dolasetron
- Anti-asthmatics (e.g. salmeterol, formoterol)
- Tacrolimus (used after organ transplant to prevent rejection)
- Certain anticancer treatments (e.g. sunitinib, nilotinib, lapatinib, sorafenib, vorinostat)

VOTRIENT is affected by food intake (see PROPER USE OF THIS MEDICATION). You should not drink grapefruit juice or eat grapefruit while you are being treated with VOTRIENT as this may increase the chance of side effects.

PROPER USE OF THIS MEDICATION

Always take VOTRIENT exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Usual dose:

The usual dose is 800 mg VOTRIENT, taken once a day.

Do not take more than 800 mg VOTRIENT a day.

Swallow the tablets whole with water, one after the other, at about the same time each day. Do not break or crush the tablets as it affects the way the medicine is absorbed and may increase the chance of side effects.

It is important that you take VOTRIENT either at least one hour before or at least two hours after food.

Depending on your response to treatment, your doctor may recommend adjusting your dose or temporarily stopping your treatment.

Overdose:

If you have accidentally taken more VOTRIENT tablets than you should, contact your doctor, or poison control centre, or go to the emergency room of the nearest hospital even if there are no symptoms.

Missed Dose:

If you forget to take VOTRIENT, do not take a double dose to make up for a missed dose. Take the next dose at the scheduled time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, VOTRIENT can cause side effects.

Very common side effects - these may affect more than 1 in 10 people:

- diarrhea (which can be severe; e.g. with fever or 3 or more times a day)
- feeling or being sick (nausea or vomiting)
- loss of appetite
- stomach pain or discomfort
- high blood pressure
- headache
- loss of strength
- lack of energy
- weakness
- changes in hair colour
- weight loss
- problems with taste
- skin rash
- a skin reaction or pain on the palms of the hands or soles of the feet (including tingling, numbness, pain, swelling or reddening)
- dizziness
- cough
- shortness of breath
- chest pain
- swelling of hands, ankles or feet
- muscle pain
- pain in the bones, muscles, ligaments, joints and tendons
- mouth sores
- unusual hair loss or thinning
- loss of skin pigment
- slow heart rate

Very common side effect that may show up in your blood tests:

- increase in some substances (enzymes) produced by the liver

Common side effects - these may affect up to 1 in 10 people:

- temporary reduction in blood supply to the brain (mini-stroke)
- reduction of blood supply to the heart (angina)
- changes in the heart's electrical conduction (QT-prolongation) which may cause irregular heartbeat
- heart attack
- severe bleeding in the lung
- under-active thyroid gland
- abnormal liver function (which can be severe and may cause yellowing of the skin or the whites of the eyes (jaundice), unusual darkening of the urine, unusual tiredness, or right upper stomach area pain)
- indigestion
- flatulence
- nosebleeds
- dry skin
- nail disorder
- skin rash
- hoarseness
- blurred vision
- chills
- urinary tract infection
- blood in the urine
- painful urination
- sudden collapse of a lung

- heart becomes less effective at pumping blood (cardiac dysfunction)
- excessive sweating
- atypical prickling or crawling sensations on the skin
- sore mouth or mouth ulcers
- blood clot in your body (you might feel chest pain, shortness of breath, leg pain, and swelling of the legs/feet). Such blood clots can break off and travel to your lungs which may be life-threatening or even fatal
- muscle spasms

Common side effects that may show up in your blood or urine tests:

- a decrease in the number of cells involved in blood clotting (thrombocytopenia)
- low white blood cell count (neutropenia, leucopenia, lymphopenia)
- protein in urine
- increase in bilirubin (a substance produced by the liver)
- decrease in albumin (a protein found in the blood)
- increase in lipase (an enzyme from the pancreas)
- increased potassium in the blood

Uncommon side effects - these may affect up to 1 in 100 people:

- stroke
- severe bleeding in digestive tract (stomach and intestine) and brain
- a dangerous rapid fluttering of the heart (Torsade de Pointes)
- hole (perforation) in digestive tract
- abnormal connection between parts of the digestive tract (fistula)
- a sudden and severe rise in blood pressure which may be life-threatening
- liver failure

Other side effects that have occurred at an uncommon rate:

- infections, with or without changes in white blood cells (cells that fight infection).
- Inflammation of the pancreas
- Separation or tear of the lining of the back part of the eye (retinal detachment or tear). This can result in trouble seeing (blurry or impaired vision).

Other side effects that have occurred rarely - these may affect up to 1 in 1000 people:

- blood clots accompanied by a decrease in red blood cells and cells involved in clotting. These clots may harm organs such as the brain and kidneys.

Side Effects with Unknown Frequency:

- Interstitial lung disease, a form of lung scarring or inflammation, can have a fatal outcome in some cases. If you develop symptoms such as sudden difficulty of breathing associated with cough or fever contact your doctor immediately.
- reversible swelling in the rear part of the brain that can be associated with high blood pressure and can lead to headache, loss of speech or vision, abnormal drowsiness, confusion and/or seizure (Posterior Reversible Encephalopathy Syndrome or Reversible Posterior Leukoencephalopathy Syndrome)

If you get side effects tell your doctor or pharmacist if any of the side effects listed becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Very common			
chest pain		✓	
Common			
diarrhea		✓	
symptoms of abnormal liver function (see above); -if yellowing of the skin or eyes appears		✓	✓
increased blood pressure		✓	
temporary reduction in blood supply to the brain (mini-stroke)		✓	
reduction of blood supply to the heart (angina)		✓	
blood clots causing chest pain, shortness of breath, leg pain, swelling of the legs/feet		✓	
decreased amount of blood pumped out of the heart with symptoms such as shortness of breath, fatigue, swollen feet and ankles		✓	
Uncommon			
severe bleeding in digestive tract (stomach and intestine) or lung			✓
heart problems, which may cause irregular heartbeat; -with symptoms of dizziness or palpitations		✓	✓
-if you experience seizures, fainting or loss of consciousness		✓	
stroke		✓	
Rare			
Blood clots accompanied by a decrease in red blood cells and			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
cells involved in clotting			
Blurry or impaired vision		✓	
Unknown Frequency			
Cough, shortness of breath, fever (interstitial lung disease)		✓	
Headaches, seizures, loss of speech or vision, high blood pressure, abnormal drowsiness			✓

This is not a complete list of side effects. For any unexpected effects while taking VOTRIENT, *contact your doctor or pharmacist.*

HOW TO STORE IT

Keep out of the reach and sight of children. Do not use VOTRIENT after the expiry date.

Store between 15 º C - 30º C.

If you have any unwanted tablets do not put them in waste water or household rubbish. Ask your pharmacist how to dispose of tablets you do not need. This will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca or by contacting the sponsor,

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This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: July 30, 2015

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