NOVARTIS

VOTRIENT

(pazopanib)

200 and 400 mg film-coated tablets

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VOTRIENT ® 200 mg tablets

VOTRIENT ® 400 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains pazopanib hydrochloride equivalent to 200 mg or 400 mg pazopanib free base.

Sugar-free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VOTRIENT 200 mg: A modified capsule-shaped, pink, film-coated tablet. One side plain and the opposite side debossed with an identifying code, GS JT.

VOTRIENT 400 mg: A modified capsule-shaped, white, film-coated tablet. One side plain and the opposite side debossed with an identifying code, GS UHL.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

VOTRIENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC) in adults.

VOTRIENT 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.

Efficacy and safety have only been established in certain STS histological tumour subtypes (see section 5.1).

4.2 Posology and method of administration

Posology:

VOTRIENT is for the use as a single chemotherapeutic medicine and is not for concurrent administration with other chemotherapeutic medicines.

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

VOTRIENT should be taken whole with water and must not be broken or crushed (see section 5.2).

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

Dose Modifications:

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 daily dose of VOTRIENT should not exceed 800 mg.

Special Populations

Paediatric population *(below 18 years)*:

The safety and efficacy of VOTRIENT in children have not been established (see section 4.4).

Elderly:

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

Renal Impairment:

Renal impairment is not expected to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section 5.2). Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 ml/min. 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.

Hepatic Impairment:

The safety and pharmacokinetics of VOTRIENT in patients with pre-existing hepatic impairment have not been fully established (see section 4.4).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (see Pharmacological Properties- Pharmacokinetic properties: special populations).

The dose of VOTRIENT should be reduced to 200 mg per day in patients with moderate hepatic impairment (see Pharmacological Properties).

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 x ULN regardless of the ALT value).

Cases of hepatic failure including fatal outcome have occurred in patients treated with VOTRIENT (see section 4.8).

Method of administration:

VOTRIENT should be taken without food (at least one hour before or two hours after a meal) (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active component and other ingredients contained in the product.

Pre-clinical studies in animals have shown reproductive toxicity. Based on animal reproduction studies and its mechanism of action, VOTRIENT can cause foetal harm when administered to a pregnant woman.

4.4 Special warnings and precautions for use

Hepatic Effects: Cases of hepatic failure (including fatalities) have been reported during use of VOTRIENT. In clinical trials with VOTRIENT, increase in serum transaminases (ALT, aspartate aminotransferase (AST)) and bilirubin were observed (see Undesirable effects). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years may be at greater risk for ALT > 3 X ULN. Patients who carry the HLA-B*57:01 allele also have an increased risk of VOTRIENT-associated ALT elevations. Liver function should be monitored in all subjects receiving VOTRIENT, regardless of genotype or age (see section 5.1). 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).

Serum liver tests should be performed before initiation of treatment with VOTRIENT, at weeks 3, 5, 7 and 9, then at months 3 and 4 with additional tests as clinically indicated. Periodic testing should then continue after month 4.

- 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 return 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 of re-initiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce VOTRIENT at a reduced dose of 400 mg once daily and perform serum liver tests weekly for 8 weeks (see section 4.2). Following re-introduction 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) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, 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.

Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations (see section 4.5) and should be undertaken with caution and close monitoring.

Beyond recommending that patients with mild hepatic impairment are treated with 800 mg VOTRIENT once daily and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with pre-existing hepatic impairment.

Hypertension: In clinical studies with VOTRIENT, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well controlled prior to initiating VOTRIENT 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 Posology and method of administration and Undesirable effects). Hypertension (systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 100 mm Hg) occurs 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). In the case of persistent hypertension despite antihypertensive therapy, VOTRIENT dose may be reduced (see section 4.2). 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.

Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS): PRES/RPLS has been reported in association with VOTRIENT. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. Permanently discontinue VOTRIENT in patients developing PRES/RPLS.

Interstitial lung disease (ILD)/Pneumonitis ILD: which can be fatal, has been reported in association with VOTRIENT (see section 4.8). Monitor patients for pulmonary symptoms

indicative of ILD/pneumonitis and discontinue VOTRIENT in patients developing ILD or pneumonitis.

Cardiac dysfunction: In clinical trials with VOTRIENT, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. In a randomized RCC trial of VOTRIENT myocardial dysfunction was observed in 13 % (47/362) of subjects in the VOTRIENT Congestive heart failure was observed in 0.5 % of subjects. In the Phase III STS clinical trial, congestive heart failure was reported in 3 out of 240 subjects (1%). In this trial decreases in LVEF in subjects 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 subjects in the VOTRIENT arm had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk (e.g., those with prior anthracycline therapy) by increasing cardiac after-load. 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). 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.

QT Prolongation and Torsade de Pointes: In clinical studies with VOTRIENT, events of QT prolongation or Torsade de Pointes have occurred (see section 4.8). VOTRIENT should be used with caution in patients with a history of QT interval prolongation, patients taking anti-dysrhythmics or other medications that may potentially prolong QT interval, or in patients with

relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

Arterial Thrombotic Events: In clinical studies with VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (see section 4.8). Fatal events have been observed. 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. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

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 %).

Thrombotic microangiopathy (TMA): Thrombotic microangiopathy (TMA) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan (see section 4.8). VOTRIENT should be permanently discontinued in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. VOTRIENT is not indicated for use in combination with other agents.

Haemorrhagic events: In clinical studies with VOTRIENT, haemorrhagic events have been reported (see section 4.8). Fatal haemorrhagic events have occurred. VOTRIENT has not been studied in patients who had a history of haemoptysis, cerebral haemorrhage, or clinically significant gastrointestinal haemorrhage in the past 6 months. VOTRIENT should be used with caution in patients with significant risk of haemorrhage.

Gastrointestinal Perforations and Fistula: In clinical studies with VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred (see section 4.8). Fatal perforation events have occurred. VOTRIENT should be used with caution in patients at risk for GI perforation or fistula.

Wound Healing: No formal studies of 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.

Hypothyroidism: In clinical studies with VOTRIENT, events of hypothyroidism have occurred (see section 4.8). Proactive monitoring of thyroid function tests is recommended.

Proteinuria: In clinical studies with VOTRIENT, proteinuria has been reported (see section 4.8). Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. VOTRIENT should be discontinued if the patient develops nephrotic syndrome.

Tumour lysis syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with VOTRIENT (see section 4.8). Patients generally at risk of TLS are those with rapidly growing tumours, a high tumour burden, renal dysfunction, or dehydration. Preventative measures such as treatment of high uric acid levels and intravenous hydration should be considered prior to initiation of VOTRIENT. Patients at risk should be closely monitored and treated as clinically indicated.

Infections: Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported.

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.

Juvenile animal toxicity: Because the mechanism of action of VOTRIENT can severely affect organ growth and maturation during early post-natal development, VOTRIENT should not be given to human paediatric patients younger than 2 years of age.

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity (see section 4.6).

Based on animal reproduction studies and its mechanism of action, VOTRIENT can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a foetus. Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT (see section 4.6).

Class effects

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in VOTRIENT.

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with VOTRIENT should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with VOTRIENT should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Interactions

Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to VOTRIENT (see section 4.5). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P gp or BCRP should be considered.

Grapefruit juice should be avoided as it also inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

4.5 Interaction with other medicines and other forms of interaction

Medicines 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 CYP3, P-gp and BCRP. Concurrent administration of VOTRIENT (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 VOTRIENT alone (400 mg once daily for 7 days). Pazopanib C_{max} and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg. Therefore, a dose reduction to 400 mg VOTRIENT once daily in the presence of strong CYP3A4 inhibitors will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg VOTRIENT once daily alone. Some patients however may have systemic VOTRIENT exposure greater than what has been observed after administration of 800 mg VOTRIENT alone.

Co-administration of VOTRIENT with strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice should be avoided as it also inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

Administration of 1 500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp and BCRP with 800 mg VOTRIENT resulted in an approximately 50 % to 60 % increase in mean pazopanib $AUC_{(0-24)}$ and C_{max} compared to administration of 800 mg VOTRIENT alone. Co-administration of VOTRIENT with a CYP3A4, Pgp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations.

Concomitant use of VOTRIENT with a strong CYP3A4 inhibitor should be avoided. If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of

VOTRIENT should be reduced to 400 mg daily during concomitant administration (see Special Warnings and Precautions for use). Further dose reduction may be considered if possible drug-related adverse events are observed.

Combination with strong P-gp or BCRP inhibitors should be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Selection of an [alternate] alternative concomitant medication with no or minimal enzyme induction potential is recommended.

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 pazopanib 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. Pazopanib 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 dextrometrophan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration 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.

Effects of VOTRIENT on other enzymes and transporters:

In vitro studies also showed that VOTRIENT is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1,2 and 0,79 µM, respectively. VOTRIENT may increase concentrations of drugs primarily eliminated through UGT1A1 and OATP1B1.

Effect of concomitant use of VOTRIENT and simvastatin:

Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT > 3 X ULN 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 simvastatin develops ALT elevations, follow guidelines for VOTRIENT posology and discontinue simvastatin (see Section 4.4)

Effect of Food on VOTRIENT:

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 (see Section 4.2).

Medicines that raise gastric pH:

Concomitant administration of VOTRIENT with esomeprazole decreases the bioavailability of pazopanib by approximately 40 % (AUC and C_{max}), and co-administration of VOTRIENT with medicines that increase gastric pH should be avoided.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Females of reproductive potential should be advised to use effective contraception during treatment with VOTRIENT and for at least 2 weeks after the last dose.

Male patients (including those who have had vasectomies) with female partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms while taking VOTRIENT and for at least 2 weeks after the last dose.

Pregnancy

VOTRIENT should not be used during pregnancy (See section 4.3)

There are no adequate data from the use of VOTRIENT in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Women of childbearing potential should use adequate contraception and should not become pregnant while receiving treatment with VOTRIENT.

Breastfeeding

Because of the potential for serious adverse reactions in breastfed infants from VOTRIENT, breastfeeding should be discontinued during treatment with VOTRIENT. (see section 4.6)

Fertility

Based on findings from animal studies, VOTRIENT may impair fertility in males and females of reproductive potential while receiving treatment.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile especially fatigue and possible blurred vision of VOTRIENT should be borne in mind when considering the patient's ability to perform task that require judgment, motor and cognitive skills.

4.8 Undesirable effects

The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a randomised, double-blind, placebo-controlled multi-centre study. Patients with locally advanced and/or metastatic RCC were randomised to receive VOTRIENT 800 mg once daily (N=290) or placebo (N=145). The median duration of treatment was 7,4 months for the VOTRIENT arm and 3,8 months for the placebo arm.

The safety and efficacy of VOTRIENT in soft tissue sarcoma (STS) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. 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.

Adverse medicine reactions from clinical trials (Table 1) are listed by MedDRA system organ class. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Adverse medicine reactions, by organ class and frequency, reported in RCC (VEG105192) and STS (VEG110727) studies

Adverse drug reactions	**Frequency classification**	
	RCC **N=290**	**STS** **N=240**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	♦	Very common
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Common	Common
Metabolism and nutrition disorders		

Anorexia	Very common	Very common
Weight decreased	Common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Insomnia	♦	Common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cardiac disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Bradycardia (asymptomatic)	Very common†	Very common†
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Common	♦
QT prolongation*	Common	Common
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Cerebral haemorrhage*	Uncommon	Uncommon
Epistaxis	Common	Common
Gastrointestinal haemorrhage*	Common	Common
Haematuria	Common	Uncommon
Hypertension*	Very common	Very common
Pulmonary haemorrhage*	Uncommon	Common

Venous thromboembolic events*	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Lipase elevations	Common‡	♦
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Alanine aminotransferase increased*	Very common	Common
Aspartate aminotransferase increased*	Very common	Common
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common

Exfoliative rash	♦	Very common
Hair depigmentation	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia syndrome (Foot-hand syndrome)	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Very common
Myalgia	♦	Very common
Renal and urinary disorders		
Proteinuria*	Common	Uncommon
General disorders and administration site conditions		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	♦	Common
Fatigue	Very common	Very common
Oedema peripheral	♦	Very common
Vision blurred	♦	Common

** - See WARNINGS AND SPECIAL PRECAUTIONS for additional information.*

♦ - Adverse event was not considered causally related to VOTRIENT in the pivotal clinical trial for this indication.

Note: Laboratory findings which met the CTC-AE criteria were recorded as adverse events at the discretion of the Investigator

† - Frequency based on heart rate measurement (< 60 beats per minute) rather than adverse event reports. Symptomatic bradycardia has been identified rarely based on a review of the VOTRIENT safety database .

‡ - For RCC, the frequency category is based on data from the supportive single-arm study VEG102616.

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

Table 2 presents laboratory abnormalities occurring in ≥ 15% of patients who received VOTRIENT in the pivotal RCC study. Grades are based on the NCI CTCAE.

Effect on Laboratory tests

During the clinical trials in patients with RCC (study VEG105192) and STS (study VEG110727), VOTRIENT caused several laboratory abnormalities but the majority were mild and did not require treatment adjustment. The changes in the following laboratory tests though still mild (grade 1-2), were greater than in the placebo group in ≥ 15 % of patients: Haematology (leukopenia, neutropenia, thrombocytopenia, lymphocytopenia and anaemia); chemistry (increased ALT, AST, glucose, total bilirubin, potassium and creatinine; and decreased phosphorus, calcium, sodium, magnesium and glucose).

Table 2 In RCC Selected Laboratory Abnormalities in ≥ 15 % of Patients who Received VOTRIENT and with a frequency greater than Placebo (VEG105192)

	Pazopanib (N=290)			**Placebo (N=145)**		
Parameters	**All Grades** *%*	**Grade 3** *%*	**Grade 4** *%*	**All Grades** *%*	**Grade 3** *%*	**Grade 4** *%*
Haematologic						
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

Table 3 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT in the pivotal STS study. Grades are based on the NCI CTCAE.

Table 3 In STS Selected Laboratory Abnormalities in ≥ 15 % of Patients who Received VOTRIENT and with a frequency greater than Placebo (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

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

Table 4 Adverse reactions identified during post-approval use

Infections and infestations

Infections (with or without neutropenia -see Section 4.4)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Tumour lysis syndrome (including fatal cases); see section Section 4.4

Blood and lymphatic system disorders

Polycythaemia , Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome see section Section 4.4)

Nervous system disorders

Posterior reversible encephalopathy syndrome (see section Section 4.4) cerebrovascular accident, transient ischaemic attack, ischaemic stroke

Eye disorders

Retinal detachment/tear

Respiratory, thoracic and mediastinal disorders

Interstitial lung disease (ILD)/pneumonitis (see section Section 4.4)

Gastrointestinal disorders

Flatulence, Pancreatitis

Hepatobiliary disorders

Gamma-glutamyl transpeptidase increased, Hepatic Failure (Including fatal events)

Musculoskeletal and connective tissue disorders

Arthralgia, Muscle spasms

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2 000 mg and 1 000 mg daily, respectively.

Symptoms and Signs:

There is currently limited experience with overdosage in VOTRIENT.

Treatment:

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma

proteins Treatment should be supportive and symptomatic. Cardiovascular monitoring for dysrhythmias and hypertension is required. Hepatic function should be assessed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 26 Cytostatic agents

Mechanism of action

Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor 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.

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered either as monotherapy or in combination with other agents, ALT > 5 X ULN (NCI CTC Grade

3) occurred in 19 % of HLA-B*57:01 allele carriers and in 10% of non-carriers. In this dataset, 133/2235 (6 %) of the patients carried the HLA-B*57:01 allele (see section 4.4).

Summary of clinical studies

Renal Cell Carcinoma (RCC)

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. Patients (N=435) with locally advanced and/or metastatic RCC were randomized to receive pazopanib 800 mg once daily or placebo. 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 was overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 were second line patients who had received one prior IL-2 or INF□-based therapy. The performance status (ECOG) was similar between the pazopanib and placebo groups (ECOG 0: 42 % vs. 41 %, ECOG 1: 58 % vs. 59 %). All patients had 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).

The primary analysis of the primary endpoint PFS is was based on disease assessment by independent radiological review in the entire study population (first line and second line).

Pazopanib demonstrated statistically significant improvement in PFS compared with placebo treatment in the overall study population (HR 0,46 [95 % CI, 0,34 to 0,62, p<0,0000001]), the treatment-naïve (HR 0,40 [95 % CI 0,27 to 0,60, p<0,0000001]) and cytokine pre-treated (HR 0,54 [95 % CI: 0,35, 0,84, p<0,001]) subgroups. In the overall study population, the median PFS was 9,2 months in pazopanib arm and 4,2 months in placebo arm. In treatment-naive sub-group, the median PFS was 11,1 months in pazopanib arm and 2,8 months in placebo arm. In cytokine pre-treated sub-group, the median PFS was 7,4 months in pazopanib arm and 4,2 months in placebo arm. In the overall population, the response rate was 30 % (95 % CI 25,1, 35,6) in the pazopanib arm and 3 % (95 % CI 0,5, 6,4) in placebo arm.

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 2,.9 months and 20,5 months [HR=0,91 (95 % CI: 0,71, 1,16; p=0,224)] for patients randomized to the pazopanib and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received pazopanib in the extension part of this study following disease progression. Sixty-six percent of placebo patients received post-study therapy compared to 30 % of pazopanib patients.

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 pazopanib or placebo ($p > 0,05$), indicating no negative impact of pazopanib on global quality of life.

In a Phase II study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review.

The safety, efficacy and quality of life of pazopanib versus sunitinib was evaluated in a randomized, open-label, parallel group Phase III non-inferiority study (VEG108844).

In VEG108844, patients (N=1 110) with locally advanced and/or metastatic RCC who had not received prior systemic therapy, were randomized to receive either pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6 week cycles of dosing with 4 weeks on treatment followed by 2 weeks without treatment.

The primary objective of this study was to evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib based on independent review committee (IRC) assessment. Demographic characteristics were similar between the treatment arms. Disease characteristics at initial diagnosis and at screening were balanced between the treatment arms with the majority of patients having clear cell histology and Stage IV disease.

VEG108844 achieved its primary endpoint of PFS and demonstrated that pazopanib was non-inferior to sunitinib (HR of 1,047 (95 % CI: 0.898; 1,220)), as the upper bound of the 95 % CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1,25. In pazopanib arm, median PFS was 8,4 months (95 % CI: 8,3, 10,9) and median OS was 28,3 months (95 % CI: 26,0, 35,5).

Soft tissue sarcoma (STS)

The safety and efficacy of pazopanib in STS were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients (N=369) with advanced STS who had received prior chemotherapy, including anthracycline treatment, or were unsuited for such therapy, were randomized to receive pazopanib 800 mg once daily or placebo.

Soft-tissue sarcoma (STS)

The efficacy and safety of pazopanib in STS were evaluated in a pivotal Phase III randomised, double-blind, placebo-controlled multicentre study (VEG110727). A total of 369 patients with advanced STS were randomised to receive pazopanib 800 mg once daily or placebo. Importantly, only patients with selective histological subtypes of STS were allowed to participate to the study, therefore efficacy and safety of pazopanib can only be considered established for those subgroups of STS and treatment with pazopanib should be restricted to such STS subtypes.

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), 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 (PNET), GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.

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+).

The median duration of follow-up of subjects (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 pazopanib [range 0,2 to 24,3 months].

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).

In the ITT population (246 subjects in the pazopanib arm, 123 subjects in placebo arm), a statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm. The median PFS in the placebo arm was 7,0 weeks (95 % CI: 4,4, 8,1) and in the pazopanib arm was 20,0 weeks (95 % CI: 17,9, 21,3), with a corresponding HR of 0,35 (95 % CI: 0,26, 0,48, p<0,001) as assessed by independent radiologist. The improvement in median PFS and HR with pazopanib compared with placebo in each of the histology subgroups (leiomyosarcoma, synovial sarcoma and “other” STS) was consistent with the overall population as assessed by the independent radiologist, with HR of 0,37 (95 % CI: 0,23, 0,60, p<0,001) in leiomyosarcoma subgroup, HR of 0,43 (95 % CI: 0,19, 0,98, p=0,0005) in synovial sarcoma subgroup, and HR of 0,39 (95 % CI: 0,25, 0,60, p<0,001) in ‘other’ STS subgroup.

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 pazopanib arm compared with the placebo arm (HR: 0,39; 95 % CI, 0,30 to 0,52, p <0,001).

The hazard ratio at the pre-specified interim analysis for overall survival in favor of pazopanib was not statistically significant; the median overall survival in the placebo arm was 10,4 months (95 % CI 8,7 to 12,7) and was 11,9 months (95 % CI 10,7 to 15,1) in the VOTRIENT arm; HR=0,82 (97,87 % CI: 0,59 to 1,14, p=0,156).

5.2 Pharmacokinetic properties

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. There was no consistent increase in AUC and C_{max} when the pazopanib dose increased 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 Section 4.2).

Administration of a single VOTRIENT 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 whole tablet. Therefore due to this potential for increased exposure, tablets should not be crushed (see Section 4.2).

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).

Biotransformation

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

Elimination

Pazopanib is eliminated slowly with mean half-life of 30,9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via faeces with renal elimination accounting for < 4 % of the administered dose.

Special populations

Renal impairment

In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30-150 ml/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 ml/min (see Section 4.2)

Hepatic Impairment

The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1.5 X ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 µg/ml, range 12.5 47.3 and 841.8 µg.hr/ml, range 600.4 1078) are similar to the median in patients with no hepatic impairment (49.4 µg/ml, range 17.1-85.7 and 888.2 µg.hr/ml, range 345.5-1482) (see section 4.2).

The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1,5 X to 3 X ULN regardless of the ALT values) was 200 mg once daily. The median steady-state values of C_{max} (22.4 µg/ml, range 6.4-32.9) and $AUC_{(0-24)}$ (350,0 µg.hr/ml, range 131,8-487,7) after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45 % and 39 %, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function (see section 4.2).

There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 X ULN regardless of the ALT value); therefore, use of pazopanib is not recommended in these patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core: magnesium stearate, microcrystalline cellulose, povidone (K30), sodium starch glycollate.

Tablet coating:

VOTRIENT 200 mg (Opadry Pink): hypromellose, iron oxide red (E172), macrogol/PEG 400, polysorbate 80, titanium dioxide (E171).

VOTRIENT 400 mg (Opadry White): hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the container tightly closed.

Keep out of reach of children

6.5 Nature and contents of container

VOTRIENT 200 mg tablet: Opaque, white high-density polyethylene (HDPE) round bottles with child resistant polypropylene closures and sealed with a polyethylene faced foil induction heat seal liner containing 30 or 90 tablets.

VOTRIENT 400 mg tablet: Opaque, white high-density polyethylene (HDPE) round bottles with child resistant polypropylene closures and sealed with a polyethylene faced foil induction heat seal liner containing 30 or 60 tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.
Magwa Crescent West,
Waterfall City,
Jukskei view,
Johannesburg,
2090
011 346 6600

8. REGISTRATION NUMBERS

VOTRIENT 200 mg: 44/26/0348

VOTRIENT 400 mg: 44/26/0349

9. DATE OF FIRST AUTHORISATION

02 October 2014

10. DATE OF REVISION OF THE TEXT

31 March 2025

2015-PSB/GLC-0772-s | 2016-PSB/GLC-0839-s | 2016-PSB/GLC-0813-s | 2017-PSB/GLC-0891-s | 2019-PSB-GLC-1084-e