NOVARTIS

Regulatory Affairs

VOTRIENT®

(pazopanib)

200 mg and 400 mg Film-coated tablets

International Package Leaflet

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VOTRIENT®

Antineoplastic agents – Protein kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Film-coated tablet

Active substance(s)

Each 200 mg tablet contains 216.7 mg of pazopanib hydrochloride, which is equivalent to 200 mg of pazopanib as free base.

Each 400 mg tablet contains 433.4 mg of pazopanib hydrochloride, which is equivalent to 400 mg of pazopanib as free base.

Excipients

Tablet core

Magnesium stearate; microcrystalline cellulose; povidone (K30); sodium starch glycollate

Tablet coating

US and Canada 200 mg (Opadry Grey): Hypromellose; Iron Oxide Black (E172); Macrogol/ PEG 400; Polysorbate 80; Titanium dioxide (E171)

200 mg (Opadry Pink): Hypromellose; Iron Oxide Red (E172); Macrogol/PEG 400; Polysorbate 80; Titanium dioxide (E171)

400 mg (Opadry White): Hypromellose; Macrogol/PEG 400; Polysorbate 80; Titanium dioxide (E171)

INDICATIONS

Renal cell carcinoma (RCC)

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

Soft tissue sarcoma (STS)

Votrient is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.

The Phase III trial population excluded patients with gastrointestinal stromal tumor (GIST) or adipocytic STS.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

The recommended dose of Votrient is 800 mg orally once daily (see Method of administration).

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

Renal impairment

Renal impairment is not expected to have a clinically relevant effect on Votrient pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section CLINICAL PHARMACOLOGY, Pharmacokinetics, Elimination). 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 hemodialysis; 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 WARNINGS AND PRECAUTIONS).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (see section CLINICAL PHARMACOLOGY).

The dose of Votrient should be reduced to 200 mg per day in patients with moderate hepatic impairment (see section CLINICAL PHARMACOLOGY).

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

Pediatric patients (below 18 years)

Votrient is not recommended for use in children and adolescents under 18 years. (see sections WARNINGS AND PRECAUTIONS and NON-CLINICAL SAFETY DATA).

Geriatric patients (above 65 years)

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

Method of administration

Votrient should be taken without food (at least one hour before or two hours after a meal) (see sections INTERACTIONS and CLINICAL PHARMACOLOGY). Votrient should be taken

whole with water and must not be broken or crushed (see section CLINICAL PHARMACOLOGY, Pharmacokinetics). If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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 section ADVERSE DRUG REACTIONS). 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 of age 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 CLINICAL PHARMACOLOGY). 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.

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 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 reinitiating Votrient treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce Votrient at a reduced dose of 400 mg once daily and perform serum liver tests weekly for 8 weeks (see section DOSAGE REGIMEN 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) 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 INTERACTIONS) 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 sections DOSAGE REGIMEN AND ADMINISTRATION and ADVERSE DRUG REACTIONS). 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). 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. Votrient should be permanently discontinued in patients developing PRES/RPLS.

Interstitial lung disease (ILD)/Pneumonitis

ILD, which can be fatal, has been reported in association with Votrient (see section ADVERSE DRUG REACTIONS). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and Votrient should be discontinued 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 compared with sunitinib, in subjects who had baseline and follow-up LVEF measurements, myocardial dysfunction was observed in 13% (47/362) of subjects in the Votrient arm compared to 11% (42/369) of subjects in the sunitinib arm. Congestive heart failure was observed in 0.5% of subjects in each treatment arm. 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 ADVERSE DRUG REACTIONS). Votrient should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics 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 ADVERSE DRUG REACTIONS). 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 on 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 ADVERSE DRUG REACTIONS). 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.

Hemorrhagic events

In clinical studies with Votrient, hemorrhagic events have been reported (see section ADVERSE DRUG REACTIONS). Fatal hemorrhagic events have occurred. Votrient has not been studied in patients who had a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months. Votrient should be used with caution in patients with significant risk of hemorrhage.

Aneurysms and artery dissections

Artery dissections and aneurysms have been reported in association with VEGF pathway inhibitors, including Votrient (see section ADVERSE DRUG REACTIONS). The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of

aneurysm and/or artery dissections. Before initiating Votrient, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal perforations and fistula

In clinical studies with Votrient, events of gastrointestinal (GI) perforation or fistula have occurred (see section ADVERSE DRUG REACTIONS). 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 ADVERSE DRUG REACTIONS). Proactive monitoring of thyroid function tests is recommended.

Proteinuria

In clinical studies with Votrient, proteinuria has been reported (see section ADVERSE DRUG REACTIONS). 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.

Tumor lysis syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with Votrient (see section ADVERSE DRUG REACTIONS). Patients generally at risk of TLS are those with rapidly growing tumors, a high tumor 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)), lapatinib (cervical cancer) or pembrolizumab (advanced renal cell carcinoma) 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 (see section NON-CLINICAL SAFETY DATA), Votrient should not be given to human pediatric patients younger than 2 years of age.

Pregnancy

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

Based on animal reproduction studies and its mechanism of action, Votrient can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with Votrient (see sections PREGNANCY and FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

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 INTERACTIONS). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The safety and efficacy of Votrient in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. Patients with locally advanced and/or metastatic RCC were randomized 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 reactions are listed below by MedDRA body system organ class.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug 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 drug 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		
Decreased appetite	Very common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cerebral haemorrhage*	Uncommon	Uncommon
Psychiatric disorders		
Insomnia	♦	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	♦
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Hypertension*	Very common	Very common
Venous embolism*	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Epistaxis	Common	Common
Pulmonary haemorrhage*	Uncommon	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦

Gastrointestinal fistula*	Uncommon	Uncommon
Gastrointestinal haemorrhage*	Common	Common
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair color changes	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia 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
Haematuria	Common	Uncommon
Eye disorders		
Vision blurred	♦	Common
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
Investigations		
Weight decreased	Common	Very common
Electrocardiogram QT prolonged*	Common	Common
Lipase increased	Common‡	♦
Alanine aminotransferase increased*	Very common	Common
Aspartate aminotransferase increased*	Very common	Common

* See Warnings and 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 erythrodysaesthesia 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.

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

	Votrient (N=290)			Placebo (N=145)		
Parameters	**All Grades** %	**Grade 3** %	**Grade 4** %	**All Grades** %	**Grade 3** %	**Grade 4** %
Haematological						
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 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 adverse 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 drug reactions identified during post-approval use

Infections and infestations	
Common	Infections (with or without neutropenia); see section WARNINGS AND PRECAUTIONS
Blood and lymphatic system disorders	
Uncommon	Polycythaemia

Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome); see section WARNINGS AND PRECAUTIONS
Eye disorders	
Uncommon	Retinal detachment Retinal tear
Metabolism and nutrition disorders	
Not known	Tumour lysis syndrome (including fatal cases); see section WARNINGS AND PRECAUTIONS
Nervous system disorders	
Rare	Posterior reversible encephalopathy syndrome (see section WARNINGS AND PRECAUTIONS)
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease (ILD)/pneumonitis (see section WARNINGS AND PRECAUTIONS)
Gastrointestinal disorders	
Common	Flatulence
Uncommon	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatic failure
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Muscle spasms
Vascular Disorders	
Rare	Aneurysms and artery dissections
Skin and subcutaneous tissue disorders	
Uncommon	Skin ulcer
Investigations	
Common	Gamma-glutamyl transpeptidase increased

INTERACTIONS

Drugs that inhibit or induce cytochrome P450 3A4 enzymes

In vitro studies suggested that the oxidative metabolism of Votrient 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 Votrient.

CYP3A4, P-gp, BCRP inhibitors

Pazopanib is a substrate for CYP3A4, 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 other strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice may also increase plasma concentrations of pazopanib.

Administration of 1500 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 section WARNINGS AND PRECAUTIONS). 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 alternative concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of Votrient on CYP substrates

In vitro studies with human liver microsomes showed that Votrient 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). 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 microM, 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 WARNINGS AND PRECAUTIONS). Insufficient data are available to assess the risk of concomitant administration of alternative statins and Votrient.

Drug-food/drink interactions

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 sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

PREGNANCY

Risk summary

Based on animal reproduction studies and its mechanism of action, Votrient can cause fetal harm when administered to a pregnant woman (see section CLINICAL PHARMACOLOGY). There are no adequate data from the use of Votrient in pregnant women. In animal developmental toxicity studies, oral administration of pazopanib to pregnant rats and rabbits throughout organogenesis resulted in teratogenicity and abortion at systemic exposures lower than that observed at the maximum recommended human dose of 800 mg/day (based on AUC). Votrient should be not be used during pregnancy unless the clinical condition of the woman requires treatment with Votrient. Pregnant women or females of reproductive potential should be advised of the potential risk to a fetus.

Animal data

In a female fertility and early embryonic development study in rats, post-implantation loss, embryo lethality and decreased fetal body weights were noted at dosages ≥10 mg/kg/day (approximately 0.2-fold the AUC at the MRHD of 800 mg/day) and increased pre-implantation loss and early resorptions were noted at dosages ≥30 mg/kg/day (approximately 0.4-fold the AUC at the MRHD of 800 mg/day).

In embryo-fetal development toxicity studies, pazopanib produced teratogenic effects (including cardiovascular malformations), delayed ossification, increased post-implantation loss, reduced fetal body weight and embryo lethality in rats at a dose level of ≥3 mg/kg/day (approximately 0.1-fold the AUC at the MRHD of 800 mg/day). In rabbits, maternal toxicity (body weight loss, reduced food consumption), increased post-implantation loss and abortion were observed at doses ≥30 mg/kg/day (approximately 0.007-fold the AUC at the MRHD of 800 mg/day), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated).

LACTATION

Risk summary

There is no information regarding the presence of pazopanib or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Votrient, a lactating woman should be advised not to breastfeed during treatment with Votrient.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Contraception

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.

Males

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.

Infertility

Based on findings from animal studies, Votrient may impair fertility in males and females of reproductive potential while receiving treatment (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Votrient doses up to 2,000 mg daily 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 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 center, where available. Hemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents – Protein kinase inhibitor, ATC Code: L01XE11.

Mechanism of action (MOA)

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)-alpha and –beta, 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-beta 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 tumor xenografts in mice.

Pharmacokinetics (PK)

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 Votrient dose increased above 800 mg once daily.

Systemic exposure to pazopanib is increased when administered with food. 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 sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

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 administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets should not be crushed (see section DOSAGE REGIMEN 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 to 100 microgram/mL. *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

Biotransformation/metabolism

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 feces 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 to 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 DOSAGE REGIMEN AND ADMINISTRATION).

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 microgram/mL, range 12.5 to 47.3 and 841.8 microgram.hr/mL, range 600.4 to 1,078) are similar to the median in patients with no hepatic impairment (49.4 microgram/mL, range 17.1 to 85.7 and 888.2 microgram.hr/mL, range 345.5 to 1,482) (see section DOSAGE REGIMEN AND ADMINISTRATION).

The maximally tolerated Votrient 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 microgram/mL, range 6.4 to 32.9) and $AUC_{(0-24)}$ (350.0 microgram.hr/mL, range 131.8 to 487.7) after administration of 200 mg Votrient 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 DOSAGE REGIMEN AND ADMINISTRATION).

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

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of Votrient 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 WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

Renal Cell Carcinoma (RCC)

The safety and efficacy of Votrient 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 Votrient 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-alpha-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 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 based on disease assessment by independent radiological review in the entire study population (first line and second line).

Table 5 Overall Efficacy Results in RCC by Independent Review Committee (IRC) (VEG105192)

Endpoints/ Study population	Votrient	Placebo	HR (95% CI)	P value (one-sided)
PFS	**Median (months)**			
Overall	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)	<0.0000001
Cytokine pre-treated	N=135	N=67		
	7.4	4.2	0.54 (0.35, 0.84)	<0.001
Response rate	**% (95% CI)**			

Overall	N=290 30 (25.1 ,35.6)	N=145 3 (0.5, 6.4)	-	<0.001

CI: confidence interval; HR: hazard ratio; ITT: Intent-to-treat; PFS: progression-free survival.

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.

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 ($p > 0.05$), indicating no negative impact of Votrient 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 Votrient 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 Votrient 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 Votrient to those treated with sunitinib. 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 Votrient was non-inferior to sunitinib, as the upper bound of the 95% CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1.25. Overall efficacy results are summarized in Table 6.

Table 6 Overall efficacy results (VEG108844)

Endpoint	Votrient N=557	Sunitinib N=553	HR (95% CI)
PFS Overall			

Median (months) (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.0)	
			1.047 (0.898,1.220)
Overall Survival Median (months) (95% CI)	 28.3 (26.0, 35.5)	 29.1 (25.4, 33.1)	
			0.915[a] (0.786, 1.065)

HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival based on independent review committee (IRC) assessment
[a] P value = 0.245 (2-sided)

Soft tissue sarcoma (STS)

The safety and efficacy of Votrient in STS were evaluated in a randomized, double-blind, placebo-controlled multi-center 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 Votrient 800 mg once daily or placebo.

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+). In each treatment group, there were a slightly greater percentage of subjects in the 2+ lines of prior systemic therapy for advanced disease (58% and 55% respectively for placebo and Votrient treatment arms) compared with 0 or 1 lines of prior systemic therapy (42% and 45% respectively for placebo and Votrient treatment arms). There were slightly more subjects with a WHO PS of 1 at baseline. 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 Votrient [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 is overall survival (OS).

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

Table 7 Overall efficacy results in STS by independent assessment (VEG110727)

Endpoints/Study Population	Votrient	Placebo	HR (95% CI)	P value (one-sided)
PFS				
Overall* ITT	N=246	N=123		
Median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	< 0.001
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)	-	-	-
PFS				
Leiomyosarcoma	N=109	N=49		
Median (weeks)	20.1	8.1	0.37 (0.23, 0.60)	< 0.001
Synovial sarcoma	N=25	N=13		
Median (weeks)	17.9	4.1	0.43 (0.19, 0.98)	0.005
'Other' STS	N=112	N=61		
Median (weeks)	20.1	4.3	0.39 (0.25, 0.60)	< 0.001

HR = Hazard ratio; ITT = Intent to treat; PFS = Progression-free survival; CR = Complete Response; PR = Partial Response.

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).

The hazard ratio at the pre-specified interim analysis for overall survival in favor of Votrient 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).

NON-CLINICAL SAFETY DATA

Safety pharmacology and repeat dose toxicity

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 - fold the AUC at the MRHD of 800 mg/day).

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.

Carcinogenicity and mutagenicity

In two year carcinogenicity studies with pazopanib, there were increased numbers of liver adenomas noted in mice and duodenal adenocarcinomas noted in rats. Based on the rodent-specific pathogenesis and mechanism for these findings, they are not considered to represent an increased carcinogenic risk for patients taking Votrient.

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).

Fertility

In female rats, reduced fertility (including increased pre- and post-implantation loss and early resorptions) was noted at dosages ≥10 mg/kg/day (approximately 0.2-fold the AUC at the MRHD of 800 mg/day). Decreased corpora lutea were noted in monkeys given 500 mg/kg/day

for up to 34 weeks, in mice given ≥100 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-fold the AUC at the MRHD of 800 mg/day, 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-fold the AUC at the MRHD of 800 mg/day) 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-fold the AUC at the MRHD of 800 mg/day).

Reproductive toxicity

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Juvenile animal studies

In juvenile toxicity studies, when pre-weaning rats were dosed from day 9 postpartum through day 14 postpartum, pazopanib caused mortalities and abnormal organ growth/maturation in kidney, lung, liver and heart, at a dose approximately 0.1-fold the AUC at the MRHD of 800 mg/day. When post-weaning rats were dosed from day 21 postpartum to day 62 post-partum, toxicological findings were similar to adult rats at comparable exposures with changes in bone, trachea, teeth, adrenal, pancreas, stomach, duodenum, lymph node, male mammary gland and reproductive organs. In rats, weaning occurs at day 21 postpartum which approximately equates to a human pediatric age of 2 years. Human pediatric patients are at increased risk for bone and teeth effects as compared to adults, as these changes, including shortened limbs, were present in juvenile rats at ≥10 mg/kg/day (equal to approximately 0.1-0.2-fold the AUC at the MRHD of 800 mg/day) (see section WARNINGS AND PRECAUTIONS).

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Votrient should not be used after the date marked “EXP” on the pack.

Votrient must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

There are no special requirements for use or handling of this product.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: June 2021

Novartis Pharma AG, Basel, Switzerland.