

# VOTRIENT™

## Pazopanib

### Description and composition

#### Pharmaceutical form

Film-coated tablet

#### Active substance (s)

Each 200 mg tablets contain 216.7 mg of pazopanib hydrochloride, which is equivalent to 200 mg of pazopanib free base. Modified capsule-shaped, pink; with GS JT debossed on one side.

Each 400 mg tablets contain 433.4 mg of pazopanib hydrochloride, which is equivalent to 400 mg of pazopanib free base. Modified capsule-shaped, white; with GS UHL debossed on one side.

#### Excipients

Tablet core

Magnesium stearate ; microcrystalline cellulose ; Povidone (K30); Sodium starch glycollate

Tablet coating

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)

### CLINICAL INFORMATION

#### Indications

*Renal cell carcinoma (RCC)*

Votrient is indicated for the treatment of patient with advanced Renal Cell Carcinoma (RCC).

*Soft tissue sarcoma (STS)*

Votrient is indicated for the treatment of patients with Soft Tissue Sarcoma (STS) who have received prior chemotherapy.

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

#### Dosage regimen and Administration

##### Dosage regimen

##### General target population

Votrient treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. 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 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 Clinical Pharmacology, Pharmacokinetics, Elimination*). Renal Impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance  $\geq 30$  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 Warning and Precautions*).

Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring due to potentially increased exposure to the medicinal product.

The dose of Votrient should be reduced to 200 mg per day in patients with moderate hepatic impairment (*see Pharmacokinetics*). There are insufficient data in patients with severe hepatic impairment (total bilirubin  $>3$  X the upper limit of normal ULN regardless of any level of ALT); 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 Warnings and Precautions, Clinical study and Non-clinical safety data*).

#### **Geriatric patients (above 65 years)**

There are limited data of the use of pazopanib in patients aged 65 years and older. In the RCC studies of pazopanib, overall no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

#### **Method of administration**

Votrient should be taken without food (at least one hour before or 2 hours after meal) (*see Interactions and Clinical pharmacology*). Votrient should be taken whole with water and must not be broken or crushed (*see 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

Votrient is contraindicated in patients with hypersensitivity to any of the excipients and severe hepatic impairment.

## 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 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 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  $\leq 1.5$  X ULN and AST and ALT  $\leq 2$  X ULN.

- Patients with isolated ALT elevations between 3 X ULN and  $\leq 8$  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 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) hyperbilirubinaemia 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 Interactions*) and should be undertaken with caution and close monitoring.

## **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 Dosage regimen and Administration, Adverse drug reactions*). Hypertension (systolic blood pressure  $\geq$  150 mmHg or diastolic blood pressure  $\geq$  100 mmHg) 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. 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 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 randomised 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 the phase III STS clinical trials. 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 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 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 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 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.

### **Haemorrhagic events**

In clinical studies with Votrient haemorrhagic events have been reported (*see Adverse drug reactions*). Fatal hemorrhagic events have occurred. Votrient has not been studied in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. Votrient should be used with caution in patients with significant risk of haemorrhage.

### **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 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 on the effect of Votrient on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with Votrient should be stopped at least 7 days prior to scheduled surgery. The decision to resume Votrient after surgery should be based on clinical judgement of adequate wound healing. Votrient should be discontinued in patients with wound dehiscence.

### **Hypothyroidism**

In clinical studies with Votrient, events of hypothyroidism have occurred (*see Adverse drug reactions*). Proactive monitoring of thyroid function tests is recommended.

### **Proteinuria**

In clinical studies with Votrient, proteinuria has been reported (*see Adverse drug reactions*). Baseline and periodic urine analysis during treatment is 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 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 regimens. Votrient is not indicated for use in combination with other agents.

### **Juvenile animal toxicity**

Because the mechanism of action of Votrient can severely affect organ growth and maturation during early post-natal development (*see Non-clinical Safety Data*), 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 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 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 (BRCP) should be avoided due to risk of increased exposure to Votrient (*see Interactions*). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BRCP 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-centre 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-centre 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 VEG105192 n=290	STS VEG110727 n=240
<b>Neoplasms benign, malignant and unspecified (incl. cysts and polyps)</b>		
Tumour pain	♦	Very common
<b>Blood and lymphatic system disorders</b>		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
<b>Endocrine disorders</b>		
Hypothyroidism*	Common	Common

Adverse drug reactions	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	Very common	Very common
<b>Nervous system disorders</b>		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cerebral haemorrhage*	Uncommon	Uncommon
<b>Psychiatric disorders</b>		
Insomnia	♦	Common
<b>Cardiac disorders</b>		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Bradycardia (asymptomatic)	Very common <sup>†</sup>	Very common <sup>†</sup>
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Common	♦
Torsade de Pointes*	Uncommon	♦
<b>Vascular disorders</b>		
Hypertension*	Very common	Very common
Venous embolism*	Common	Common
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Epistaxis	Common	Common
Pulmonary haemorrhage*	Uncommon	Common
<b>Gastrointestinal disorders</b>		
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
<b>Hepatobiliary disorders</b>		
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
<b>Skin and subcutaneous tissue disorders</b>		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair color changes	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysesthesia syndrome	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
<b>Musculoskeletal and connective tissue disorders</b>		

Adverse drug reactions	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Musculoskeletal pain	◆	Very common
Myalgia	◆	Very common
<b>Renal and urinary disorders</b>		
Proteinuria*	Common	Uncommon
Haematuria	Common	Uncommon
<b>Eye disorders</b>		
Vision blurred	◆	Common
<b>General disorders and administration site disorders</b>		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	◆	Common
Fatigue	Very common	Very common
Oedema peripheral	◆	Very common
<b>Investigations</b>		
Weight decreased	Common	Very common
Electrocardiogram QT prolonged*	Common	Common
Lipase increased	Common <sup>‡</sup>	◆
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 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 studies. Grades are based on the NCI CTCAE.

**Table-2 Selected Laboratory Abnormalities in  $\geq 15\%$  of Patients who Received VOTRIENT and with a frequency greater than Placebo(VEG105192)**

Parameters	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
<b>Haematological</b>						
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
<b>Chemistry</b>						
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  $\geq 15\%$  of patients who received Votrient in the pivotal STS study. Grades are based on the NCI CTCAE.

**Table-3 Selected Laboratory Abnormalities in  $\geq 15\%$  of Patients who Received VOTRIENT and with a frequency greater than Placebo (VEG110727)**

Parameters	VOTRIENT (N = 240)			Placebo (N = 123)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
<b>Haematological</b>						
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
<b>Chemistry</b>						
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 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**

<b>Infections and infestations</b>	
<i>Common</i>	Infections (with or without neutropenia); (see Warnings and precautions)

**Blood and lymphatic system disorders**

<i>Uncommon</i>	Polycythaemia
<i>Uncommon</i>	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome); (see <i>Warnings and precautions</i> )

**Eye disorders**

<i>Uncommon</i>	Retinal detachment
	Retinal tear

**Metabolism and nutrition disorders**

<i>Not known</i>	Tumour lysis syndrome (including fatal cases); (see <i>Warnings and precautions</i> )
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**Nervous system disorders**

<i>Rare</i>	Posterior reversible encephalopathy syndrome (see <i>Warnings and precautions</i> )
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**Respiratory, thoracic and mediastinal disorders**

<i>Rare</i>	Interstitial lung disease (ILD)/pneumonitis (see <i>Warnings and precautions</i> )
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**Gastrointestinal disorders**

<i>Common</i>	Flatulence
<i>Uncommon</i>	Pancreatitis

**Hepatobiliary disorders**

<i>Not Known</i>	Hepatic failure
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**Musculoskeletal and connective tissue disorders**

<i>Very common</i>	Arthralgia
<i>Common</i>	Muscle spasms

**Investigations**

<i>Common</i>	Gamma-glutamyl transpeptidase increased
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**Vascular disorders**

<i>Rare</i>	Aneurysms and artery dissections
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**Skin and subcutaneous tissue disorders**

<i>Uncommon</i>	Skin ulcer
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**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<sub>(0-24)</sub> and C<sub>max</sub>, respectively, relative to administration of Votrient alone (400 mg once daily for 7 days). Pazopanib C<sub>max</sub> 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<sub>(0-24)</sub> and C<sub>max</sub> 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 inhibitors should be avoided. If no medically acceptable alternative to a strong CYP3A4 inhibitor is available, the dose of Votrient should be reduced to 400 mg daily during concomitant administration (*see 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 alternate 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<sub>max</sub> of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextrometorphan 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<sup>2</sup> (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C<sub>max</sub>, 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<sub>50</sub> 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 > 3xULN was reported in 126 / 895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin (p = 0.038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for Votrient posology and discontinue simvastatin (*see 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 Dosage regimen and Administration*).

#### **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 and 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 Clinical pharmacology*). There are no adequate data from the use of Votrient in pregnant women. Studies in animals have shown reproductive toxicity (*see Pre-clinical Safety Data*). In animal development toxicity studies, oral administration of Votrient to pregnant rats and rabbits throughout organogenesis results in teratogenicity and abortion at systemic exposure lower than that observed at the maximum recommended human dose of 800 mg/day (based on AUC). Votrient should 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 decreases fetal body weights were noted at dosages  $\geq 10$  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  $\geq 30$  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 as a dose level of  $\geq 3$  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  $\geq 30$  mg/kg/day (approximately 0.007 fold the AUC at the MRHD of 800 mg/day), while fetal weights was reduced at doses  $\geq 3$  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 in the breastfed infant, or on milk production. Because of 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 Non-clinical Safety Data*).

### **Ability to perform tasks that require judgment, motor or cognitive skills**

There have been no studies to investigate the effect of Votrient on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of Votrient should be borne in mind when considering the patient's ability to perform task that require judgment, motor and cognitive skills.

### **Overdosage**

Votrient doses up to 2,000 mg have been evaluated in clinical trials Grade 3 fatigue (dose limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 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.

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

#### **ATC Code**

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

### **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)- $\alpha$  and  $-\beta$ , and stem cell factor receptor (c-KIT), with IC<sub>50</sub> 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 tumour xenografts in mice.

## Pharmacokinetics

### 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<sub>max</sub> when the Votrient dose increased above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of Votrient with high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C<sub>max</sub>. Therefore, Votrient should be administered at least 1 hour before or 2 hours after a meal (*see Dosage regimen and Administration*).

Administration of a single Votrient 400 mg crushed tablet increased AUC<sub>(0-72)</sub> by 46% and C<sub>max</sub> by approximately 2-fold and decreased t<sub>max</sub> 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 increase after administration of the crushed tablet relative to administration of the whole tablet Therefore, due to this potential for increased exposure, tablets should not be crushed (*see Dosage 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 10-100  $\mu\text{g/ml}$ . *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 faeces with renal elimination accounting for < 4 % of the administered dose.

## Special population

### 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 creatine clearance  $\geq 30$  ml/min.

### **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  $\mu\text{g/ml}$ , range 12.5-47.3 and 841.8  $\mu\text{g}\cdot\text{hr/ml}$ , range 600.4-1078) are similar to the median in patients with no hepatic impairment (49.4  $\mu\text{g/ml}$ , range 17.1-85.7 and 888.2  $\mu\text{g}\cdot\text{hr/ml}$ , range 345.5-1482) (*see 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  $\mu\text{g/ml}$ , range 6.4-32.9) and  $AUC_{(0-24)}$  (350.0  $\mu\text{g}\cdot\text{hr/ml}$ , range 131.8-487.7) 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 Dosage regimen and Administration*).

There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 x ULN regardless of any level of ALT); 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 as either 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 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-centre 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 is 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 received one prior IL-2 or  $\text{INF}\alpha$ -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 by Independent Review Committee (IRC)(VEG105192)**

Endpoints/ Study population	VOTRIENT	Placebo	HR (95 % CI)	P value (one-sided)
<b>PFS</b>	<b>Median (months)</b>			
Overall	N=290 9.2	N=145 4.2	0.46 (0.34, 0.62)	<0.0000001
Treatment-naïve	N=155 11.1	N=78 2.8	0.40 (0.27, 0.60)	<0.0000001
Cytokine pre-treated	N=135 7.4	N=67 4.2	0.54 (0.35, 0.84)	<0.001
<b>Response rate</b>	<b>% (95 % CI)</b>			
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 2 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 has been evaluated in a randomised, open-label, parallel group Phase III non-inferiority study (VEG108844).

In VEG108844, patients (N = 1110) 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 summarised in Table 6.

**Table-6: Overall efficacy results (VEG108844)**

Endpoint	Votrient N=557	Sunitinib N=553	HR (95% CI)
<b>PFS</b>			
Overall Median (months) (95% CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.0)	
			1.047 (0.898,1.220)
<b>Overall Survival</b>			
Median (months) (95% CI)	28.3 (26.0, 35.5)	29.1 (25.4, 33.1)	
			0.915 <sup>a</sup> (0.786, 1.065)

HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival based on independent review committee (IRC) assessment

<sup>a</sup> 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-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 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)
<b>PFS</b>				
Overall* ITT	N = 246	N = 123		
Median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	< 0.001
<b>Response Rate (CR + PR)</b>				
% (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)	-	-	-
<b>PFS</b>				
<b>Leiomyosarcoma</b>	N = 109	N = 49		
Median (weeks)	20.1	8.1	0.37 (0.23, 0.60)	< 0.001
<b>Synovial sarcoma</b>	N = 25	N = 13		
Median (weeks)	17.9	4.1	0.43 (0.19, 0.98)	0.005
<b>'Other' STS</b>	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 favour 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,  $p = 0.156$ ).

### Pediatric population

A Phase II study (PZP034X2203) of pazopanib was conducted in 57 pediatric patients with refractory solid tumours including rhabdomyosarcoma (N=12), non-rhabdomyosarcoma soft tissue sarcoma (N=11), Ewing sarcoma/pPNET (N=10), osteosarcoma (N=10), neuroblastoma (N=8) and hepatoblastoma (N=6). The study was a single-agent, non-controlled, open-label study to determine the therapeutic activity of pazopanib in children and adolescents aged 1 to <18 years of age. Pazopanib was administered daily as a tablet at a dose of 450 mg/m<sup>2</sup>/dose or as an oral suspension at 225 mg/m<sup>2</sup>/dose. The maximum daily dose permitted was 800 mg for the tablet and 400 mg for the oral suspension. The median duration of exposure was 1.8 months (1 day-29 months).

Results of this study did not show any meaningful anti-tumour activity in the respective pediatric population. Pazopanib is therefore not recommended for treatment of these tumours in the pediatric population (*see section Dosage regimen and Administration*).

## **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, haematological 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  $\geq 10$  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  $\geq 100$  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  $\geq 100$  mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) following 15 weeks of dosing. Following 26 weeks of dosing, there were decreased testicular and epididymal weights, atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis of male rats given doses  $\geq 30$  mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC).

### **Reproductive toxicity**

For information on reproductive toxicity, *see Pregnancy, lactation, females and males of reproductive potential.*

### **Juvenile animal studies**

In juvenile toxicity studies, when pre-weaning rats were dosed from day 9 post partum 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 post partum 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  $\geq 10$  mg/kg/day (equal to approximately 0.1-0.2 fold the AUC at the MRHD of 800 mg/day) (see *Warnings and Precautions*).

## **Pharmaceutical Information**

### **Incompatibilities**

*Not applicable*

### **Shelf-Life**

The expiry date is indicated on the packaging.

### **Special Precautions for Storage**

Store below 30°C.

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

### **Nature and Contents of Container**

**200 mg tablet** - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 tablets.

**400 mg tablet** - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 60 tablets.

### **Instructions for Use/Handling**

*No relevant information*

Not all presentations are available in every country.

Votrient Tablet 200 mg, Box, Bottle @ 30 tablet      Reg. No.

Votrient Tablet 400 mg, Box, Bottle @ 60 tablet      Reg. No.

## **HARUS DENGAN RESEP DOKTER**

### **Manufactured by**

Novartis Pharmaceutical Manufacturing LLC, Ljubljana, Slovenia

For Novartis Pharma AG, Basel, Switzerland

### **Imported by**

PT Novartis Indonesia

Jakarta, Indonesia

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