VOTRIENT™
Pazopanib

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

200 mg Tablet

The 200 mg tablets contain 217 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base. Modified capsule-shaped, pink; with GS JT debossed on one side.

400 mg Tablet

The 400 mg tablets contain 433 mg of pazopanib hydrochloride, equivalent to 400 mg of pazopanib free base. Modified capsule-shaped, white; with GS UHL debossed on one side.

2. PHARMACEUTICAL FORM

Film-coated tablets

3. CLINICAL INFORMATION

3.1 Indications

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

3.2 Dosage and Administration

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.

VOTRIENT should be taken without food (at least one hour before or 2 hours after meal).

Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure *(see Pharmacokinetics).*

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

Dose modifications

Dose modification 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.

Paediatric patients

VOTRIENT is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

Elderly

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.

Renal impairment

Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low excretion of pazopanib and metabolites *(see Pharmacokinetics).* Therefore, no dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment

The safety and pharmacokinetics of pazopanib in patients with 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. Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation but a reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (see Pharmacokinetics).
Pazopanib is contraindicated in patients with severe hepatic impairment *(see Contraindications).*

3.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe hepatic impairment

3.4 Warnings and Precautions

Hepatic Effects: Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. The safety and pharmacokinetics of pazopanib have not been fully established in patients with pre-existing hepatic impairment. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment *(see Dosage and Administration).* Insufficient data are available in patients with mild hepatic impairment to provide a dose adjustment recommendation. Pazopanib is contraindicated in patients with severe hepatic impairment *(see Contraindications)*.
In clinical studies with pazopanib, increase in serum transaminases (ALT, AST) and billirubin were observed *(see Adverse Reactions).* In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or billirubine.

Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

- Patients with isolated transaminase elevations ≤ 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
- Patients with transaminases of > 8 X ULN should have VOTRIENT interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose and measure serum liver tests weekly for 8 weeks *(see Dosage and Administration).* If transaminase elevations > 3 X ULN recur, then VOTRIENT should be discontinued.
- If transaminase elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, bilirubin fractionation should be performed. If direct (conjugated) bilirubin is > 35 % of total bilirubin, VOTRIENT should be discontinued.

Hypertension: Blood pressure should be well controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy *(see Adverse Reactions).* Hypertension occurs early in the course of treatment (88 % occurring in first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the VOTRIENT dose may be reduced *(see Dosage and Administration).* VOTRIENT should be discontinued if hypertension is severe and persists despite anti-hypertensive therapy and VOTRIENT dose reduction.

QT Prolongation and Torsade de Pointes: In clinical studies with VOTRIENT, events of QT prolongation or Torsade de Pointes have occurred *(see Adverse Reactions).* VOTRIENT should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those with relevant pre-existing cardiac disease. When using VOTRIENT, 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 Reactions)* VOTRIENT should be used with caution in patients who are at increased risk for these events. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

Haemorrhagic Events: In clinical studies with VOTRIENT haemorrhagic events have been reported *(see Adverse Reactions).*VOTRIENT is not recommended 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.

Gastrointestinal Perforations and Fistula: In clinical studies with VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred *(see Adverse Reactions).* 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 pazopanib, events of hypothyroidism have occurred *(see Pre-clinical Safety Data).* Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Heart failure: The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure has not been studied.

Proteinuria: In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urine analysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops Grade 4 proteinuria.

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 pazopanib (see Interactions). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BRCP should be considered.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to pazopanib *(see Interactions).*
Concomitant administration of pazopanib with uridine diphosphate glucuronosyl tranferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1.
Grapefruit juice should be avoided during treatment with pazopanib *(see Interactions).*

Pregnancy: Pre-clinical studies in animals have shown reproductive toxicity *(Pre-clinical Safety Data).*

If VOTRIENT is used during pregnancy, or if the patient becomes pregnant while receiving VOTRIENT, the potential hazard to the foetus should be explained to the patient. Women of

childbearing potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT *(see Pregnancy and Lactation).*

3.5 Interactions

Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

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

CYP3A4, P-gp, BCRP inhibitors : Pazopanib is a substrate for CYP3A4, P-gp and BCRP. Concurrent administration of a single dose pazopanib eye drops with the strong CYP3A4 inhibitor, ketoconazole, in healthy volunteers resulted in 220 % and 150 % increase in mean $AUC_{(0-t)}$ and C_{max} values, respectively.

Co-administration of VOTRIENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, 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. Coadministration of VOTRIENT with a CYP3A4, Pgp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations.

Combination with strong CYP3A4 inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *(see Dosage and Administration).*

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

Based on *in vitro* IC50 and *in vivo* plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin).

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

3.6 Pregnancy and Lactation
Fertility
VOTRIENT may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed *(see Pre-clinical Safety Data).*
Pregnancy
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).* The potential risk for humans is unknown. VOTRIENT should be not be used during pregnancy unless the clinical condition of the woman requires treatment with VOTRIENT. If VOTRIENT is used during pregnancy, or if the patient becomes pregnant while receiving VOTRIENT, the potential hazard to the foetus should be explained to the patient.

Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with VOTRIENT.

Lactation
The safe use of VOTRIENT during lactation has not been established. It is not known whether pazopanib is excreted in human milk. Breast feeding should be discontinued during treatment with VOTRIENT.

Effects on ability to drive and use machines
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. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

3.7 Adverse Reactions
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.

Adverse reactions are listed below by MedDRA body system organ class.
The following convention has been utilised for the classification of frequency:
Very common ≥ 1 in 10
Common ≥ 1 in 100 and < 1 in 10
Uncommon ≥ 1 in 1,000 and < 1 in 100
Categories have been assigned based on absolute frequencies in the clinical trial data.

Blood and lymphatic system disorders	
Common	Thrombocytopenia Neutropenia

Endocrine disorders	
Common	Hypothyroidism
Metabolism and nutrition disorders	
Very common	Anorexia
Common	Weight decreased
Nervous system disorders	
Very common	Headache
Common	Transient ischaemic attack
Uncommon	Ischaemic stroke
Cardiac disorders	
Common	Myocardial ischaemia
	QT prolongation
Uncommon	Torsade de Pointes
Vascular disorders	
Very common	Hypertension
Haemorrhages	
Common	Epistaxis
	Haematuria
Uncommon	Pulmonary haemorrhage
	Gastrointestinal haemorrhage
	Cerebral haemorrhage
Respiratory, thoracic and mediastinal disorders	Chest pain
Common	
Gastrointestinal disorders	
Very common	Diarrhoea
	Nausea
	Vomiting
	Abdominal pain
Common	Dysgeusia
	Dyspepsia
Uncommon	Gastrointestinal perforation
	Gastrointestinal fistula
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased
	Aspartate aminotransferase increased
Common	Hepatic function abnormal
	Hyperbilirubinaemia

Skin and subcutaneous tissue disorders	
Very common	Hair depigmentation
Common	Rash Alopecia Skin depigmentation Palmar-plantar erythrodysaesthesia syndrome
Renal and urinary disorders	
Common	Proteinuria
General disorders and administration site conditions	
Very common	Fatigue Asthenia

Table 1 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT.

Table 1 Selected Laboratory Abnormalities in ≥15 % of Patients who Received VOTRIENT and More Commonly than Placebo Arm

	VOTRIENT (N = 290)			Placebo (N = 145)		
Parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<I	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

3.8 Overdosage

VOTRIENT doses up to 2,000 mg have been evaluated in clinical trials without dose-limiting toxicity.

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.
There is no specific antidote for overdose with VOTRIENT.

4. CLINICAL PHARMACOLOGY

4.1 Pharmacodynamics
ATC Code
Pharmacotherapeutic group: Antineoplastic agents - Protein kinase inhibitor, ATC Code: L01XE11.
Mechanism of Action
VOTRIENT is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and -β, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR- β receptors in cells. *In vivo,* pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumour xenografts in mice.

4.2 Pharmacokinetics
Absorption
Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumours, maximum plasma concentration (C_{max}) of approximately 19 ± 13 µg/ml were obtained after median 3.5 hours (range 1.0-11.9 hours) and an AUC∞ of approximately 650 ± 500 µg.h/ml was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC.

There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

Systemic exposure to pazopanib is increased when administered with food. Administration of pazopanib with high fat or low fat meal results in an approximately 2-fold increase in AUC and Cmax. Therefore, pazopanib should be administered at least two hours after food or at least one hour before food *(see Dosage and Administration).*

Administration of a pazopanib 400 mg crushed tablet increased AUC (0-72) by 46% and C_{max} by approximately 2 fold and decreased t_{max} by approximately 2 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 *(see Dosage and Administration).*

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

Metabolism
Results from *in vitro* studies demonstrated that metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6 % of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

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 : Results indicate that less than 4 % of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 ml/min to 150 ml/min) indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population *(see Dosage and Administration)*.

Hepatic impairment : In subjects with moderate hepatic impairment the median pazopanib C_{max} and AUC(0-6 hr) normalized to a dose of 800 mg once daily were both increased 2-fold compared to those in subjects with normal hepatic function. Based on safety, tolerability and pharmacokinetic data, the dosage of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment *(see Dosage and Administration).* Data are not available in subjects with mild hepatic impairment. Pazopanib is contraindicated in patients with severe hepatic impairment *(see Contraindications).*

4.3 Clinical Studies
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 naive and 202 were second line patients who received one prior IL-2 or INFα-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-naive 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 2 Overall Efficacy Results by Independent Review Committee (IRC)

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-naive	N=155	N=78		
	1 1 . 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	N=145		
	30 (25.1 ,35.6)	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.

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.

4.4 PRE-CLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with VOTRIENT have not been performed, mice given 1,000 mg/kg/day (approximately 2.5 times the human clinical exposure based on AUC) for 13 weeks had proliferative lesions noted in the liver including eosinophilic foci in 2 females and a single case of adenoma in another female.

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

In female rats, reduced fertility including increased pre- and post-implantation loss, early resorptions, were noted at dosages ≥10 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). 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, 2.2 and 1.4 times the human clinical exposure based on AUC, respectively).

Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at ≥100 mg/kg/day (approximately 0.8 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 ≥30 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC).

Pazopanib produced foetal teratogenic effects (including cardiovascular malformations and delayed ossification), reduced foetal body weight, and embryo lethality in rats at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC). In rabbits, maternal toxicity (body weight loss, reduced food consumption, and abortion) were observed at doses ≥30 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC),

while foetal weight was reduced at doses ≥3 mg/kg/day. *(see Pregnancy and Lactation, Warnings and Precautions).*

Animal Toxicology and/or Pharmacology

In toxicology studies in rats, there were effects in a variety of tissues (bone, teeth, bone marrow, nail beds, reproductive organs, 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 times the human clinical exposure based on AUC).

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 1.0 times the human clinical exposure, respectively.

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5.1 List of Excipients
Tablet Core *- **200 mg and 400 mg***
Magnesium stearate, Microcrystalline cellulose, Povidone (K30), Sodium starch glycollate

Tablet film-coat - 200 mg (Opadry Pink)
Hypromellose, Iron Oxide Red (EI72), Macrogol / PEG 400, Polysorbate 80, Titanium dioxide (EI71)

Tablet film-coat 400 mg (Opadry White)
Hypromellose, Macrogol / PEG 400, Polysorbate 80, Titanium dioxide (E171)

5.2 Incompatibilities
No known incompatibilities.

5.3 Shelf-Life
The expiry date is indicated on the packaging.

5.4 Special Precautions for Storage
Do not store above 30°C.

5.5 Nature and Contents of Container
200 mg tablet - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 90 tablets.
400 mg tablet - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 60 tablets.

5.6 Instructions for Use/Handling

No relevant information

Votrient is a trademark of the GlaxoSmithKline group of companies.

Not all presentations are available in every country.

Votrient Tablet 200 mg, Box, Bottle @ 30 tablet	Reg. No. DKI1075704517A1
Votrient Tablet 200 mg, Box, Bottle @ 90 tablet	Reg. No. DKI1075704517A1
Votrient Tablet 400 mg, Box, Bottle @ 30 tablet	Reg. No. DKI1075704517B1

Votrient Tablet 400 mg, Box, Bottle @ 60 tablet Reg. No. DKI1075704517B1

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