EFFICACY AND SAFETY RESULTS FROM PRINCIPAL:

A **REAL-WORLD** STUDY OF VOTRIENT IN ADVANCED RCC

A global, multicenter, long-term, prospective, observational study of VOTRIENT® (pazopanib) tablets (N=484) for the treatment of advanced RCC.[1]

This brochure contains data that are not contained in, but are consistent with, the Prescribing Information for VOTRIENT. These data are based on a prospective, observational study and, therefore, are subject to limitations.

The primary objective of the PRINCIPAL study was to evaluate the real-world effectiveness and safety of VOTRIENT in patients with advanced RCC.[1]

Indication

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

Important Safety Information for VOTRIENT® (pazopanib) tablets

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.
See "Warnings and Precautions," Section 5.1, in full Prescribing Information.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient®
pazopanib tablets (200 mg)

PRINCIPAL: A Prospective, Observational Study of VOTRIENT in Advanced RCC[1]

These data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT® (pazopanib) tablets in patients with advanced RCC.

Data exclude a population that was not consistent with the phase 3 pivotal trial.

OBJECTIVES

1. To evaluate PFS, OS, and ORR.
2. To evaluate the frequency of serious AEs and AEs of special interest.

STUDY DESIGN

- A global, multicenter, long-term, prospective, observational study to evaluate treatment patterns and clinical outcomes in patients with advanced RCC treated for the first time with VOTRIENT
- Study included real patients and was not a retrospective chart review
- The study population included male and female patients (≥18 years of age) with a documented diagnosis of clear cell or predominantly clear cell RCC
- Patients initiated treatment within 30 days of enrollment and participated for 30 months or until discontinuation

KEY ELIGIBILITY CRITERIA
- ≥18 years
- Documented diagnosis of advanced RCC
- Clear cell or predominantly clear cell histology
- Clinical decision to initiate treatment with VOTRIENT

TREATMENT
- VOTRIENT 200 mg to 800 mg once daily for 30 months or until discontinuation (N=484)

PRIMARY EFFICACY END POINTS
- PFS
- OS
- ORR

AE, adverse event; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Hepatic Toxicity and Hepatic Impairment: Severe and fatal hepatotoxicity has occurred. Patients older than 65 years are at an increased risk. Increases in serum transaminase levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and bilirubin were observed. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). In patients with preexisting moderate hepatic impairment, the starting dose of VOTRIENT should be reduced to 200 mg per day or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution *[**see** **Drug Interactions**]*. Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.**

Baseline Patient Demographics and Disease Characteristics[1]

Data exclude a population that was not consistent with the phase 3 pivotal trial.

	All patients (N=484)
Median age, years (range)	66 (22-90)
Sex, n (%)	
Male	333 (69)
Female	151 (31)
Race, n (%)	
White	455 (94)
African American/African	2 (0.4)
Asian	3 (0.6)
Hispanic	10 (2)
Other	14 (3)
Median number of metastatic sites	2
Location of metastatic sites, n (%)	
Lung	304 (63)
Bone	136 (28)
Liver	71 (15)
Adrenal glands	47 (10)
Lymph nodes	166 (34)
Other	134 (28)
Histology, n (%)	
Clear cell	431 (89)
Predominantly clear cell	53 (11)
ECOG performance status, n (%)	
0	262 (54)
1	222 (46)
First-line systemic therapy	
Yes	26 (5)
No	458 (95)

ECOG, Eastern Cooperative Oncology Group.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

QT Prolongation and Torsades de Pointes: Prolonged QT intervals and arrhythmias, including torsades de pointes, have occurred. Use with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant preexisting cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (eg, calcium, magnesium, potassium) within the normal range should be performed.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient®
pazopanib tablets (200 mg)

Risk Criteria Evolved Over Time[2-4]

- Highlighted sections of the table below show differences in risk criteria used in the phase 3 pivotal and PRINCIPAL trials

Phase 3 Pivotal Trial		PRINCIPAL Trial	
MSKCC 1999	Risk Factors	MSKCC 2002	IMDC 2009
✔	Hgb <LLN or ≤13 g/dL (men) or ≤11.5 g/dL (women)	✔	✔
✔	Corrected calcium >10 mg/dL	✔	✔
✔	KPS <80%	✔	✔
✔	Lactate dehydrogenase >300 U/L	✔	
✔	No prior nephrectomy		
	Time from initial diagnosis to IFN-α or other treatment <1 year	✔	✔
	Absolute neutrophil count >ULN		✔
	Platelets >ULN		✔
	Risk Group		
0	Favorable	0	0
1-2	Intermediate	1-2	1-2
3-5	Poor	3-5	3-6

- There are several differences in risk criteria used to stratify patients in the phase 3 pivotal (MSKCC 1999) and PRINCIPAL trials (MSKCC 2002 and IMDC 2009)
  - These evolved criteria may help account for the differences between risk groups in the 2 trials

Hgb, hemoglobin; IFN-α; interferon-alpha; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; LLN, lower limit of normal; MSKCC, Memorial Sloan Kettering Cancer Center; ULN, upper limit of normal.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Cardiac Dysfunction: Cardiac dysfunction, such as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF), has occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 0.6% (4/586) of patients without routine on-study LVEF monitoring. In a randomized RCC trial of VOTRIENT® (pazopanib) tablets compared with sunitinib, in patients who had baseline and follow-up LVEF measurements, myocardial dysfunction occurred in 13% (47/362) of patients on VOTRIENT compared with 11% (42/369) of patients on sunitinib. CHF occurred in 0.5% of patients on each arm. Monitor blood pressure (BP), and manage promptly using a combination of antihypertensive therapy and dose modification of VOTRIENT (interruption and reinitiation at a reduced dose based on clinical judgment). Carefully monitor patients for clinical signs or symptoms of CHF. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction, including previous anthracycline exposure.

Patients by Risk Stratification Across Trials and Criteria

PATIENTS ACROSS ALL RISK GROUPS WERE INCLUDED IN THE PRINCIPAL AND PHASE 3 PIVOTAL TRIALS[1,5]

Data exclude a population that was not consistent with the phase 3 pivotal trial.

- In the pivotal trial, the majority of patients were MSKCC favorable and intermediate risk
- In the PRINCIPAL trial, the majority of patients were MSKCC and IMDC intermediate risk

	Phase 3 Pivotal Trial (VOTRIENT n=290)	PRINCIPAL Trial (N=484)	
	MSKCC 1999	MSKCC 2002	IMDC 2009
Favorable, n (%)	113 (39)	21 (4)	28 (6)
Intermediate, n (%)	159 (55)	302 (62)	286 (59)
Poor, n (%)	9 (3)	39 (8)	83 (17)

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Hemorrhagic Events: Fatal hemorrhagic events were reported in 0.9% (5/586) of patients in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT compared to 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). VOTRIENT should not be used in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal (GI) hemorrhage in the past 6 months.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient® pazopanib tablets (200 mg)

Median PFS According to Risk Status in the PRINCIPAL Trial

PRINCIPAL data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT® (pazopanib) tablets in patients with advanced RCC.

PRINCIPAL data exclude a population that was not consistent with the phase 3 pivotal trial.

- **ALL PATIENTS:** Median overall **PFS of 12.4 months** with VOTRIENT (N=484) (95% CI, 10.7-14.8)[1]

MEDIAN PROGRESSION-FREE SURVIVAL[1]

	Median PFS, months (95% CI)	
	MSKCC 2002	IMDC 2009
Favorable	**25.4** (9.8-NR) n=21	**26** (12-31.2) n=28
Intermediate	**12.3** (9.6-15.9) n=302	**12.6** (10.7-16.4) n=286
Poor	**6.6** (3.0-8.5) n=39	**6.3** (3.7-9.2) n=82

A prospective, observational study of VOTRIENT in patients with advanced RCC (N=484) of clear cell or predominantly clear cell histology. Primary efficacy end points were PFS, OS, and ORR.

IN THE VOTRIENT PHASE 3 PIVOTAL TRIAL:

- 11.1 months median PFS in first-line patients vs 2.8 months with placebo (HR=0.40 [95% CI, 0.27-0.60], *P*<0.001) was observed in the phase 3 pivotal trial for VOTRIENT, as described in the full Prescribing Information[6]

CI, confidence interval; HR, hazard ratio; NR, not reached.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Arterial Thromboembolic Events: Arterial thromboembolic events have been observed, including fatal events (0.3%, 2/586) in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. Use with caution in patients who are at increased risk for these events or have a history of these events. Do not use VOTRIENT in patients who have had an arterial thromboembolic event in the past 6 months.

Median Overall Survival Outcomes in the PRINCIPAL Trial

PRINCIPAL data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT in patients with advanced RCC.

PRINCIPAL data exclude a population that was not consistent with the phase 3 pivotal trial.

- **ALL PATIENTS:** Median overall **OS of 33.9 months** with VOTRIENT (N=484) (95% CI, 30.3-NR)[1]

MEDIAN OVERALL SURVIVAL OUTCOMES[1]

	Median OS, months (95% CI)	
	MSKCC 2002	IMDC 2009
Favorable	**NR** (29.7-NR) n=21	**NR** n=28
Intermediate	**33.9** (30.3-NR) n=302	**33.9** (33.9-NR) n=286
Poor	**14.6** (6.3-23.7) n=39	**14.6** (8.7-23.1) n=83

- Median OS not reached in favorable-risk patients in the PRINCIPAL trial[1]

IN THE VOTRIENT PHASE 3 PIVOTAL TRIAL:

- 22.9 months median OS vs 20.5 months with placebo (HR=0.91 [95% CI, 0.71-1.16]) was observed in the phase 3 pivotal trial for VOTRIENT, as described in the full Prescribing Information[6]
  - Crossover permitted for disease progression for patients in the placebo arm

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Venous Thromboembolic Events (VTEs): VTEs have occurred, including venous thrombosis and fatal pulmonary emboli. In the randomized RCC trial, VTEs were reported in 1% of patients treated with VOTRIENT and in 1% of patients treated with placebo. Monitor for signs and symptoms.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient® pazopanib tablets (200 mg)

ORR and Median Duration of Response in the PRINCIPAL Trial

PRINCIPAL data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT® (pazopanib) tablets in patients with advanced RCC.

PRINCIPAL data exclude a population that was not consistent with the phase 3 pivotal trial.

- **ALL PATIENTS: 33% ORR** with VOTRIENT (n=132)[1]
- **ALL PATIENTS: Median DoR of 14 months** with VOTRIENT (95% CI, 8.9-17.2)[1]

MEDIAN DURATION OF RESPONSE THAT LASTED FOR MORE THAN 1 YEAR[1]

	Median DoR, months (95% CI)	
	MSKCC 2002	IMDC 2009
Favorable	**18** (6.1-25)	**21** (9.1-26.4)
Intermediate	**14** (8.9-20.5)	**14** (7.5-18.4)
Poor	**3** (0-14.6)	**17** (4.1-24.6)

IN THE VOTRIENT PHASE 3 PIVOTAL TRIAL:

- A 32% ORR vs 4% with placebo in first-line patients[5]
- A 13-month (58.7 weeks) median duration of response (95% CI, 52.1-68.1 weeks), as described in the full Prescribing Information[6]

DoR, duration of response.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

Thrombotic Microangiopathy (TMA): TMA, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated.

PRINCIPAL: Consistent Safety and Tolerability Profile

PRINCIPAL data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT in patients with advanced RCC.

PRINCIPAL data exclude a population that was not consistent with the phase 3 pivotal trial.

MOST COMMON DRUG-RELATED ARs OCCURRING IN ≥10% OF PATIENTS IN THE PRINCIPAL TRIAL[1]

Primary system organ class preferred term	All grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Number of subjects with at least 1 event	301 (62.2)	130 (26.9)	8 (1.7)
Gastrointestinal disorders	94 (19.4)	23 (4.8)	0
Diarrhea	62 (12.8)	16 (3.3)	0
Investigations	128 (26.4)	44 (9.1)	1 (0.2)
ALT increased	61 (12.6)	25 (5.2)	0
Vascular disorders	114 (23.6)	42 (8.7)	1 (0.2)
Hypertension	109 (22.5)	40 (8.3)	0

One patient experienced a grade 5 AR of disease progression.

- Most common grade 3/4 ARs were ALT increased (5%) and hypertension (8%)[1]

IN THE VOTRIENT PHASE 3 PIVOTAL TRIAL:

- ARs that occurred in ≥10% of patients who received VOTRIENT included diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), anorexia (22%), vomiting (21%), fatigue (19%), asthenia (14%), abdominal pain (11%), and headache (10%)[6]
- The most common grade 3/4 laboratory abnormalities were ALT and AST increases (12% and 7%, respectively)[6]

PRINCIPAL DISCONTINUATION RATE CONSISTENT WITH PHASE 3 PIVOTAL TRIAL

- 15% of patients taking VOTRIENT discontinued due to an AR in both the PRINCIPAL and phase 3 pivotal trials[1,7]

AR, adverse reaction.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient® pazopanib tablets (200 mg)

Indication

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

Important Safety Information for VOTRIENT® (pazopanib) tablets

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. *See "Warnings and Precautions," Section 5.1, in full Prescribing Information.*

Hepatic Toxicity and Hepatic Impairment: Severe and fatal hepatotoxicity has occurred. Patients older than 65 years are at an increased risk. Increases in serum transaminase levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and bilirubin were observed. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). In patients with preexisting moderate hepatic impairment, the starting dose of VOTRIENT should be reduced to 200 mg per day or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution *[**see Drug Interactions**]*. Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.**

QT Prolongation and Torsades de Pointes: Prolonged QT intervals and arrhythmias, including torsades de pointes, have occurred. Use with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant preexisting cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (eg, calcium, magnesium, potassium) within the normal range should be performed.

Cardiac Dysfunction: Cardiac dysfunction, such as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF), has occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 0.6% (4/586) of patients without routine on-study LVEF monitoring. In a randomized RCC trial of VOTRIENT compared with sunitinib, in patients who had baseline and follow-up LVEF measurements, myocardial dysfunction occurred in 13% (47/362) of patients on VOTRIENT compared with 11% (42/369) of patients on sunitinib. CHF occurred in 0.5% of patients on each arm. Monitor blood pressure (BP), and manage promptly using a combination of antihypertensive therapy and dose modification of VOTRIENT (interruption and reinitiation at a reduced dose based on clinical judgment). Carefully monitor patients for clinical signs or symptoms of CHF. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction, including previous anthracycline exposure.

Hemorrhagic Events: Fatal hemorrhagic events were reported in 0.9% (5/586) of patients in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT compared to 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). VOTRIENT should not be used in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal (GI) hemorrhage in the past 6 months.

Arterial Thromboembolic Events: Arterial thromboembolic events have been observed, including fatal events (0.3%, 2/586) in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. Use with caution in patients who are at increased risk for these events or have a history of these events. Do not use VOTRIENT in patients who have had an arterial thromboembolic event in the past 6 months.

Venous Thromboembolic Events (VTEs): VTEs have occurred, including venous thrombosis and fatal pulmonary emboli. In the randomized RCC trial, VTEs were reported in 1% of patients treated with VOTRIENT and in 1% of patients treated with placebo. Monitor for signs and symptoms.

Thrombotic Microangiopathy (TMA): TMA, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated.

GI Perforation and Fistula: In RCC trials, GI perforation or fistula was reported in 0.9% (5/586) of patients receiving VOTRIENT. Fatal perforation events occurred in 0.3% (2/586) of these patients. Use with caution in patients at risk for these events, and monitor for signs and symptoms.

Interstitial Lung Disease (ILD)/Pneumonitis: ILD/pneumonitis, which can be fatal, has been reported in 0.1% of patients in the clinical trials treated with VOTRIENT. Monitor patients for ILD/pneumonitis, and discontinue VOTRIENT if symptoms of ILD or pneumonitis develop.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has been reported and may be fatal. Permanently discontinue VOTRIENT in patients developing RPLS.

Hypertension (HTN): HTN, including hypertensive crisis, has occurred in clinical trials. HTN occurs early in the course of treatment (approximately 40% of cases occurred by Day 9, and 90% of cases occurred in the first 18 weeks). BP should be well controlled prior to initiating VOTRIENT, monitored early after starting treatment (no longer than 1 week), and frequently thereafter. Treat increased BP promptly with standard antihypertensive therapy and dose reduction or interruption of VOTRIENT, as clinically warranted. Discontinue VOTRIENT if there is evidence of hypertensive crisis or if HTN is severe and persistent despite antihypertensive therapy and dose reduction of VOTRIENT. Approximately 1% of patients required permanent discontinuation of VOTRIENT because of HTN.

Wound Healing: VOTRIENT may impair wound healing. Interruption of therapy is recommended in patients undergoing surgical procedures. Treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. VOTRIENT should be discontinued in patients with wound dehiscence.

Hypothyroidism: Hypothyroidism was reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial and in no patients receiving placebo. Monitoring of thyroid function tests is recommended.

Proteinuria: In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving VOTRIENT, leading to discontinuation of treatment in 2 patients.

Important Safety Information for VOTRIENT® (pazopanib) tablets (cont)

There were no reports of proteinuria in patients receiving placebo. Monitor urine protein at baseline and periodically as clinically indicated. Interrupt treatment for 24-hour urine protein ≥3 grams, and discontinue for repeat episodes despite dose reductions.

Tumor Lysis Syndrome (TLS): Cases of TLS, including fatal cases, have been reported in patients with RCC treated with VOTRIENT. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis, and treat as clinically indicated.

Infection: Serious infections (with or without neutropenia), some with fatal outcomes, have been reported. Monitor for signs and symptoms, and treat active infection promptly. Consider interruption or discontinuation of VOTRIENT.

Increased Toxicity With Other Cancer Therapy: VOTRIENT is not indicated for use in combination with other agents. Increased toxicity and mortality have been observed in clinical trials administering VOTRIENT in combination with lapatinib or with pemetrexed. The fatal toxicities observed included pulmonary hemorrhage, GI hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.

Increased Toxicity in Developing Organs: The safety and effectiveness of VOTRIENT in pediatric patients have not been established. VOTRIENT is not indicated for use in pediatric patients. Animal studies have demonstrated pazopanib can severely affect organ growth and maturation during early postnatal development, and resulted in toxicity to the lungs, liver, heart, and kidney, and in death. VOTRIENT may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

Females and Males of Reproductive Potential: VOTRIENT can cause fetal harm when administered to a pregnant woman based on animal reproduction studies and its mechanism of action. In animal developmental and reproductive toxicology 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.

Verify pregnancy status of females of reproductive potential prior to starting treatment with VOTRIENT. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of VOTRIENT. To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, advise male patients (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with VOTRIENT and for at least 2 weeks after the last dose. VOTRIENT may impair fertility in females and males of reproductive potential while receiving treatment. Because of the potential for serious adverse reactions in breastfed infants from VOTRIENT, advise a lactating woman not to breastfeed during treatment with VOTRIENT and for 2 weeks after the final dose.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their health care provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact.

Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. In the RCC trials of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients.

Pneumothorax: Two of 290 patients treated with VOTRIENT and no patients on the placebo arm in the randomized RCC trial developed a pneumothorax.

Bradycardia: In the randomized trial of VOTRIENT for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with VOTRIENT and in 11% (16/144) of patients on the placebo arm.

Drug Interactions: Coadministration with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin) increases concentrations of pazopanib and should be avoided, but, if warranted, reduce the dose of VOTRIENT to 400 mg. Avoid grapefruit and grapefruit juice.

Concomitant use of strong CYP3A4 inducers (eg, rifampin) should be avoided due to the potential to decrease concentrations of pazopanib. VOTRIENT should not be used in patients who cannot avoid chronic use of CYP3A4 inducers.

Concomitant treatment with strong inhibitors of P-glycoprotein (PgP) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib.

CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. If a patient develops ALT elevations, follow dosing guidelines for VOTRIENT, consider alternatives to VOTRIENT, or consider discontinuing simvastatin. Insufficient data exist to assess the risk of concomitant administration of alternative statins and VOTRIENT.

Drugs That Raise Gastric pH: Avoid concomitant use of VOTRIENT with drugs that raise gastric pH (eg, esomeprazole) due to the potential to decrease concentrations of pazopanib. Consider short-acting antacids in place of proton pump inhibitors (PPIs) and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours.

Adverse Reactions in the Randomized RCC Trial: A dose interruption was required for 42% of patients on VOTRIENT. The VOTRIENT dose was reduced for 36% of patients.

The most common adverse reactions (≥20%) for VOTRIENT vs placebo were diarrhea (52% vs 9%), HTN (40% vs 10%), hair color changes (depigmentation) (38% vs 3%), nausea (26% vs 9%), anorexia (22% vs 10%), and vomiting (21% vs 8%).

Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in patients taking VOTRIENT vs placebo included increases in ALT (53% vs 22%), AST (53% vs 19%), glucose (41% vs 33%), and total bilirubin (36% vs 10%); decreases in phosphorus (34% vs 11%), sodium (31% vs 24%), magnesium (26% vs 14%), and glucose (17% vs 3%); and leukopenia (37% vs 6%), neutropenia (34% vs 6%), thrombocytopenia (32% vs 5%), and lymphocytopenia (31% vs 24%).

In a pooled analysis of VOTRIENT clinical trials, East Asian patients had a higher frequency of neutropenia, thrombocytopenia, and palmar-plantar erythrodysesthesia syndrome than non-East Asian patients. *(See Adverse Reactions, Section 6.1, in full Prescribing Information.)*

Please click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Votrient®
pazopanib tablets (200 mg)

EFFICACY AND SAFETY RESULTS FROM PRINCIPAL:

A **Real-World** Study of VOTRIENT in Advanced RCC

PRINCIPAL data are based on a prospective, observational study and, therefore, are subject to limitations. The primary objective of the PRINCIPAL study is to evaluate the real-world effectiveness and safety of VOTRIENT® (pazopanib) tablets in patients with advanced RCC.

PRINCIPAL data exclude a population that was not consistent with the phase 3 pivotal trial.

EFFICACY RESULTS FROM THE PRINCIPAL TRIAL

- 1-year **median PFS** with VOTRIENT (**12.4 months**; [95% CI, 10.7-14.8])[1]
- More than 2.5 years **median OS** with VOTRIENT (**33.9 months**; [95% CI, 30.3-NR])[1]
- **Median duration of response** that lasted **14 months** (95% CI, 8.9-17.2)[1]

SAFETY RESULTS FROM THE PRINCIPAL TRIAL

- Safety and tolerability were consistent with the well-characterized safety profile of VOTRIENT[1]
- Most common ARs were hypertension, diarrhea, and ALT increased[1]
- 15% discontinuation rate consistent with phase 3 pivotal trial[1]

IN THE VOTRIENT PHASE 3 PIVOTAL TRIAL:

- 11.1 months median PFS with VOTRIENT in first-line patients vs 2.8 months with placebo (HR=0.40 [95% CI, 0.27-0.60], *P*<0.001)[6]
- 22.9 months median OS with VOTRIENT vs 20.5 months with placebo (HR=0.91 [95% CI, 0.71-1.16])[6]
- A 58.7-week median duration of response (95% CI, 52.1-68.1)[6]
- The most common ARs (≥20%) for VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting[6]

Indication

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

Important Safety Information for VOTRIENT® (pazopanib) tablets

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. *See "Warnings and Precautions," Section 5.1, in full Prescribing Information.*

References: 1. Data on file. Novartis Pharmaceuticals Corp; 2018. **2.** Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999;17(8):2530-2540. **3.** Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol.* 2002;20(1):289-296. **4.** Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009;27(34):5794-5799. **5.** Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28(6):1061-1068. **6.** Votrient [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. **7.** Data on file. Novartis Pharmaceuticals Corp; 2011.

Please see additional Important Safety Information throughout and on pages 10 and 11, and click here for full Prescribing Information, including Boxed WARNING, and Medication Guide.

NOVARTIS

Votrient® pazopanib tablets (200 mg)

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080