

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-465**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VOTRIENT safely and effectively. See full prescribing information for VOTRIENT.

VOTRIENT (pazopanib) tablets

Initial U.S. Approval: 2009

### WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. [See Warnings and Precautions (5.1).]

### INDICATIONS AND USAGE

VOTRIENT is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma. (1)

### DOSAGE AND ADMINISTRATION

- 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal). (2.1)
- Baseline moderate hepatic impairment – 200 mg orally once daily. Not recommended in patients with severe hepatic impairment. (2.2)

### DOSAGE FORMS AND STRENGTHS

200 mg and 400 mg tablets. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Increases in serum transaminase levels and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Measure liver chemistries before the initiation of treatment and regularly during treatment. (5.1)
- Prolonged QT intervals and torsades de pointes have been observed. Use with caution in patients at higher risk of developing QT interval prolongation. Monitoring electrocardiograms and electrolytes should be considered. (5.2)
- Fatal hemorrhagic events have been reported. VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients. (5.3)
- Arterial thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for these events. (5.4)

- Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. (5.5)
- Hypertension has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. (5.6)
- Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. (5.7)
- Hypothyroidism may occur. Monitoring of thyroid function tests is recommended. (5.8)
- Proteinuria: Monitor urine protein. Discontinue for Grade 4 proteinuria. (5.9)
- VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT. (5.10, 8.1)

### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 20\%$ ) are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- CYP3A4 Inhibitors: Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors. (7.1)
- CYP3A4 Inducers: Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT. (7.1)
- CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: October 2009  
VTR:xPI

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1

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: HEPATOTOXICITY**

4 **Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic**  
5 **function and interrupt, reduce, or discontinue dosing as recommended. [See Warnings and**  
6 **Precautions (5.1).]**

7 **1 INDICATIONS AND USAGE**

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

10 **2 DOSAGE AND ADMINISTRATION**

11 **2.1 Recommended Dosing**

12 The recommended dose of VOTRIENT is 800 mg orally once daily without food (at least  
13 1 hour before or 2 hours after a meal) [see *Clinical Pharmacology (12.3)*]. The dose of  
14 VOTRIENT should not exceed 800 mg.

15 Do not crush tablets due to the potential for increased rate of absorption which may affect  
16 systemic exposure. [See *Clinical Pharmacology (12.3)*.]

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

18 **2.2 Dose Modification Guidelines**

19 Initial dose reduction should be 400 mg, and additional dose decrease or increase should  
20 be in 200 mg steps based on individual tolerability. The dose of VOTRIENT should not exceed  
21 800 mg.

22 Hepatic Impairment: The dosage of VOTRIENT in patients with moderate hepatic  
23 impairment should be reduced to 200 mg per day. There are no data in patients with severe  
24 hepatic impairment; therefore, use of VOTRIENT is not recommended in these patients. [See  
25 *Use in Specific Populations (8.6)*.]

26 Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4  
27 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations  
28 and should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce  
29 the dose of VOTRIENT to 400 mg. Further dose reductions maybe needed if adverse effects  
30 occur during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed  
31 without inhibitors. However, there are no clinical data with this dose adjustment in patients  
32 receiving strong CYP3A4 inhibitors. [See *Drug Interactions (7.1)*.]

33 Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4  
34 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided.  
35 VOTRIENT should not be used in patients who can not avoid chronic use of strong CYP3A4  
36 inducers. [See *Drug Interactions (7.1)*.]

37 **3 DOSAGE FORMS AND STRENGTHS**

38 200 mg tablets of VOTRIENT — modified capsule-shaped, gray, film-coated with GS JT  
39 debossed on one side. Each tablet contains 216.7 mg of pazopanib hydrochloride equivalent to  
40 200 mg of pazopanib.

41 400 mg tablets of VOTRIENT — modified capsule-shaped, yellow, film-coated with  
42 GS UHL debossed on one side. Each tablet contains 433.4 mg of pazopanib hydrochloride  
43 equivalent to 400 mg of pazopanib.

44 **4 CONTRAINDICATIONS**

45 None.

46 **5 WARNINGS AND PRECAUTIONS**

47 **5.1 Hepatic Effects**

48 In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum  
49 transaminases (ALT, AST) and bilirubin, was observed [*see Adverse Reactions (6.1)*]. This  
50 hepatotoxicity can be severe and fatal. Transaminase elevations occur early in the course of  
51 treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks).  
52 Across all monotherapy studies with VOTRIENT, ALT >3 X upper limit of normal (ULN) was  
53 reported in 138/977 (14%) and ALT >8 X ULN was reported in 40/977 (4%) of patients who  
54 received VOTRIENT. Concurrent elevations in ALT >3 X ULN and bilirubin >2 X ULN  
55 regardless of alkaline phosphatase levels were detected in 13/977 (1%) of patients. Four of the 13  
56 patients had no other explanation for these elevations. Two of 977 (0.2%) patients died with  
57 disease progression and hepatic failure.

- 58 • Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once  
59 every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic  
60 monitoring should then continue after this time period.
- 61 • Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on  
62 VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or  
63 baseline.
- 64 • Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted  
65 until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with  
66 VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce  
67 VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver  
68 tests weekly for 8 weeks [*see Dosage and Administration (2.2)*]. Following reintroduction of  
69 VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently  
70 discontinued.
- 71 • If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN,  
72 VOTRIENT should be permanently discontinued. Patients should be monitored until  
73 resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated)  
74 hyperbilirubinemia may occur in patients with Gilbert's syndrome [*see Clinical*  
75 *Pharmacology (12.5)*]. Patients with only a mild indirect hyperbilirubinemia, known

76 Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the  
77 recommendations outlined for isolated ALT elevations.

78 The safety of VOTRIENT in patients with pre-existing severe hepatic impairment,  
79 defined as total bilirubin >3 X ULN with any level of ALT, is unknown. Treatment with  
80 VOTRIENT is not recommended in patients with severe hepatic impairment. [See *Dosage and*  
81 *Administration (2.2) and Use in Specific Populations (8.6).*]

## 82 **5.2 QT Prolongation and Torsades de Pointes**

83 In clinical RCC studies of VOTRIENT, QT prolongation ( $\geq 500$  msec) was identified on  
84 routine electrocardiogram monitoring in 11/558 (<2%) of patients. Torsades de pointes occurred  
85 in 2/977 (<1%) of patients who received VOTRIENT in the monotherapy studies.

86 In the randomized clinical trial, 3 of the 290 patients receiving VOTRIENT had post-  
87 baseline values between 500 to 549 msec. None of the 145 patients receiving placebo had post-  
88 baseline QTc values  $\geq 500$  msec.

89 VOTRIENT should be used with caution in patients with a history of QT interval  
90 prolongation, in patients taking antiarrhythmics or other medications that may prolong QT  
91 interval, and those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline  
92 and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium,  
93 magnesium, potassium) within the normal range should be performed.

## 94 **5.3 Hemorrhagic Events**

95 In clinical RCC studies of VOTRIENT, hemorrhagic events have been reported [all  
96 Grades (16%) and Grades 3 to 5 (2%)]. Fatal hemorrhage has occurred in 5/586 (0.9%) [see  
97 *Adverse Reactions (6.1)*]. VOTRIENT has not been studied in patients who have a history of  
98 hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months  
99 and should not be used in those patients.

## 100 **5.4 Arterial Thrombotic Events**

101 In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke,  
102 and transient ischemic attack [all Grades (3%) and Grades 3 to 5 (2%)] were observed. Fatal  
103 events have been observed in 2/586 (0.3%). In the randomized study, these events were observed  
104 more frequently with VOTRIENT compared to placebo [see *Adverse Reactions (6.1)*].

105 VOTRIENT should be used with caution in patients who are at increased risk for these events or  
106 who have had a history of these events. VOTRIENT has not been studied in patients who have  
107 had an event within the previous 6 months and should not be used in those patients.

## 108 **5.5 Gastrointestinal Perforation and Fistula**

109 In clinical RCC studies of VOTRIENT, gastrointestinal perforation or fistula has been  
110 reported in 5 patients (0.9%). Fatal perforation events have occurred in 2/586 (0.3%). Monitor  
111 for symptoms of gastrointestinal perforation or fistula.

## 112 **5.6 Hypertension**

113 Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should  
114 be monitored for hypertension and treated as needed with anti-hypertensive therapy.

115 Hypertension (systolic blood pressure  $\geq 150$  or diastolic blood pressure  $\geq 100$  mm Hg) was

116 observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in  
117 the course of treatment (88% occurred in the first 18 weeks). [See *Adverse Reactions (6.1)*.] In  
118 the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT  
119 may be reduced [see *Dosage and Administration (2.2)*]. VOTRIENT should be discontinued if  
120 hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of  
121 VOTRIENT.

## 122 **5.7 Wound Healing**

123 No formal studies on the effect of VOTRIENT on wound healing have been conducted.  
124 Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may  
125 impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to  
126 scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical  
127 judgment of adequate wound healing. VOTRIENT should be discontinued in patients with  
128 wound dehiscence.

## 129 **5.8 Hypothyroidism**

130 In clinical RCC studies of VOTRIENT, hypothyroidism reported as an adverse reaction  
131 in 26/586 (4%) [see *Adverse Reactions (6.1)*]. Proactive monitoring of thyroid function tests is  
132 recommended.

## 133 **5.9 Proteinuria**

134 In clinical RCC studies with VOTRIENT, proteinuria has been reported in 44/586 (8%)  
135 [Grade 3, 5/586 (<1%) and Grade 4, 1/586 (<1%)] [see *Adverse Reactions (6.1)*]. Baseline and  
136 periodic urinalysis during treatment is recommended. VOTRIENT should be discontinued if the  
137 patient develops Grade 4 proteinuria.

## 138 **5.10 Pregnancy**

139 VOTRIENT can cause fetal harm when administered to a pregnant woman. Based on its  
140 mechanism of action, VOTRIENT is expected to result in adverse reproductive effects. In pre-  
141 clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and  
142 abortifacient.

143 There are no adequate and well-controlled studies of VOTRIENT in pregnant women. If  
144 this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the  
145 patient should be apprised of the potential hazard to the fetus. Women of childbearing potential  
146 should be advised to avoid becoming pregnant while taking VOTRIENT. [See *Use in Specific*  
147 *Populations (8.1)*.]

# 148 **6 ADVERSE REACTIONS**

## 149 **6.1 Clinical Trials Experience**

150 Because clinical trials are conducted under widely varying conditions, adverse reaction  
151 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
152 trials of another drug and may not reflect the rates observed in practice.

153 Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT  
 154 prolongation and torsades de pointes, hemorrhagic events, arterial thrombotic events, and  
 155 gastrointestinal perforation and fistula [see Warnings and Precautions (5.1-5.5)].

156 The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies  
 157 which included 586 patients with RCC. With a median duration of treatment of 7.4 months  
 158 (range 0.1 to 27.6), the most commonly observed adverse reactions ( $\geq 20\%$ ) in the 586 patients  
 159 were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting.

160 The data described below reflect the safety profile of VOTRIENT in 290 RCC patients  
 161 who participated in a randomized, double-blind, placebo-controlled study [see Clinical Studies  
 162 (14)]. The median duration of treatment was 7.4 months (range 0 to 23) for patients who  
 163 received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent  
 164 (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of  
 165 patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions  
 166 occurring in  $\geq 10\%$  of patients who received VOTRIENT.

167  
 168 **Table 1. Adverse Reactions Occurring in  $\geq 10\%$  of Patients who Received VOTRIENT**

Adverse Reactions	VOTRIENT			Placebo		
	(N = 290)			(N = 145)		
	All Grades <sup>a</sup>	Grade 3	Grade 4	All Grades <sup>a</sup>	Grade 3	Grade 4
	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

169 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

170  
 171 Other adverse reactions observed more commonly in patients treated with VOTRIENT  
 172 than placebo and that occurred in  $< 10\%$  (any grade) were alopecia (8% versus  $< 1\%$ ), chest pain  
 173 (5% versus 1%), dysgeusia (altered taste) (8% versus  $< 1\%$ ), dyspepsia (5% versus  $< 1\%$ ), facial  
 174 edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus  
 175  $< 1\%$ ), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%),  
 176 and weight decreased (9% versus 3%).

177 Table 2 presents the most common laboratory abnormalities occurring in >10% of  
 178 patients who received VOTRIENT and more commonly (≥5%) in patients who received  
 179 VOTRIENT versus placebo.  
 180

181 **Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received**  
 182 **VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus**  
 183 **Placebo**

Parameters	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades <sup>a</sup>	Grade 3	Grade 4	All Grades <sup>a</sup>	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Hematologic</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
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

184 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.  
 185

186 **Hepatic Toxicity:** In a controlled clinical study with VOTRIENT for the treatment of  
 187 RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups,  
 188 respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in  
 189 <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2  
 190 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of  
 191 patients on VOTRIENT and 2/145 (1%) on placebo. [See *Dosage and Administration (2.2)* and  
 192 *Warnings and Precautions (5.1)*.]

193 **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC,  
 194 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo  
 195 experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving  
 196 VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of  
 197 hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290

198 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension.  
199 In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on  
200 VOTRIENT. [See Warnings and Precautions (5.2).]

201 **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with  
202 VOTRIENT, QT prolongation ( $\geq 500$  msec) was identified on routine electrocardiogram  
203 monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on  
204 placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in  
205 the RCC studies. [See Warnings and Precautions (5.3).]

206 **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the  
207 incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)],  
208 cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher  
209 in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). [See  
210 Warnings and Precautions (5.4).]

211 **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients  
212 (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1  
213 hemorrhagic event. The most common hemorrhagic events in the patients treated with  
214 VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage  
215 (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced  
216 serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four  
217 (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145)  
218 (0%) patients on placebo. [See Warnings and Precautions (5.5).] In the overall safety population  
219 in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients  
220 treated with VOTRIENT.

221 **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a  
222 shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the  
223 normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27%  
224 compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19  
225 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. [See Warnings  
226 and Precautions (5.7).]

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

231 **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been  
232 reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients,  
233 proteinuria led to discontinuation of treatment with VOTRIENT.

234 **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were  
235 observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for  
236 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC  
237 studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%).

238 **7 DRUG INTERACTIONS**

239 **7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

243 **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4  
244 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose  
245 reduction for VOTRIENT should be considered when it must be coadministered with strong  
246 CYP3A4 inhibitors [see *Dosage and Administration (2.2)*]. Grapefruit juice should be avoided as  
247 it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

248 **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib  
249 concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can  
250 not be avoided [see *Dosage and Administration (2.2)*].

251 **7.2 Effects of Pazopanib on CYP Substrates**

252 Results from drug-drug interaction studies conducted in cancer patients suggest that  
253 pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on  
254 CYP1A2, CYP2C9, or CYP2C19 [see *Clinical Pharmacology (12.3)*].

255 Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are  
256 metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may  
257 result in inhibition of the metabolism of these products and create the potential for serious  
258 adverse events. [See *Clinical Pharmacology (12.3)*.]

259 **8 USE IN SPECIFIC POPULATIONS**

260 **8.1 Pregnancy**

261 Pregnancy Category D [see *Warnings and Precautions (5.10)*].

262 VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no  
263 adequate and well-controlled studies of VOTRIENT in pregnant women.

264 In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic,  
265 fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis  
266 at a dose level of  $\geq 3$  mg/kg/day (approximately 0.1 times the human clinical exposure based on  
267 AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal  
268 subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or  
269 absent ossification. In addition, there was reduced fetal body weight, and pre- and post-  
270 implantation embryoletality in rats administered pazopanib at doses  $\geq 3$  mg/kg/day. In rabbits,  
271 maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion)  
272 was observed at doses  $\geq 30$  mg/kg/day (approximately 0.007 times the human clinical exposure).  
273 In addition, severe maternal body weight loss and 100% litter loss were observed at doses  
274  $\geq 100$  mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at  
275 doses  $\geq 3$  mg/kg/day (AUC not calculated).

276 If this drug is used during pregnancy, or if the patient becomes pregnant while taking this  
277 drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing  
278 potential should be advised to avoid becoming pregnant while taking VOTRIENT.

### 279 **8.3 Nursing Mothers**

280 It is not known whether this drug is excreted in human milk. Because many drugs are  
281 excreted in human milk and because of the potential for serious adverse reactions in nursing  
282 infants from VOTRIENT, a decision should be made whether to discontinue nursing or to  
283 discontinue the drug, taking into account the importance of the drug to the mother.

### 284 **8.4 Pediatric Use**

285 The safety and effectiveness of VOTRIENT in pediatric patients have not been  
286 established.

287 In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week  
288 administration, toxicities in bone, teeth, and nail beds were observed at doses  $\geq 3$  mg/kg/day  
289 (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day  
290 (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13-  
291 and 26-week studies with rats. Body weight loss and morbidity were observed at these doses.  
292 Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or  
293 absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle,  
294 broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in  
295 rats at  $\geq 30$  mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at  
296 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks.

### 297 **8.5 Geriatric Use**

298 In clinical trials with VOTRIENT for the treatment of RCC, 196 subjects (33%) were  
299 aged  $\geq 65$  years, and 34 subjects (6%) were aged  $>75$  years. No overall differences in safety or  
300 effectiveness of VOTRIENT were observed between these subjects and younger subjects.  
301 However, patients  $>60$  years of age may be at greater risk for an ALT  $>3$  X ULN. Other reported  
302 clinical experience has not identified differences in responses between elderly and younger  
303 patients, but greater sensitivity of some older individuals cannot be ruled out.

### 304 **8.6 Hepatic Impairment**

305 The safety and pharmacokinetics of pazopanib in patients with hepatic impairment have  
306 not been fully established. In clinical studies for VOTRIENT, patients with total bilirubin  $\leq 1.5$  X  
307 ULN and AST and ALT  $\leq 2$  X ULN were included [*see Warnings and Precautions (5.1)*].

308 An interim analysis of data from 12 patients with normal hepatic function and 9 with  
309 moderate hepatic impairment showed that the maximum tolerated dose in patients with moderate  
310 hepatic impairment was 200 mg per day [*see Clinical Pharmacology (12.3)*]. There are no data  
311 on patients with severe hepatic impairment [*see Dosage and Administration (2.2)*].

### 312 **8.7 Renal Impairment**

313 Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance  
314  $\geq 30$  mL/min) were included in clinical studies for VOTRIENT.

315 There are no clinical or pharmacokinetic data in patients with severe renal impairment or  
316 in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is  
317 unlikely to significantly affect the pharmacokinetics of pazopanib since <4% of a radiolabeled  
318 oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408  
319 subjects with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance  
320 of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and  
321 dose adjustment is not necessary.

## 322 10 OVERDOSAGE

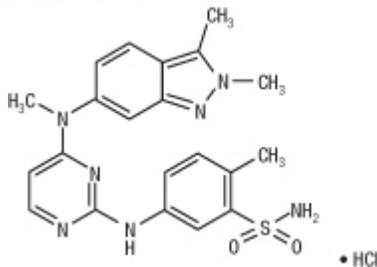
323 Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting  
324 toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed  
325 at 2,000 mg daily and 1,000 mg daily, respectively.

326 Treatment of overdose with VOTRIENT should consist of general supportive measures.  
327 There is no specific antidote for overdosage of VOTRIENT.

328 Hemodialysis is not expected to enhance the elimination of VOTRIENT because  
329 pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

## 330 11 DESCRIPTION

331 VOTRIENT (pazopanib) is a tyrosine kinase inhibitor (TKI). Pazopanib is presented as  
332 the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-  
333 yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. It has  
334 the molecular formula  $C_{21}H_{23}N_7O_2S \cdot HCl$  and a molecular weight of 473.99. Pazopanib  
335 hydrochloride has the following chemical structure:



336 Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at  
337 pH 1 and practically insoluble above pH 4 in aqueous media.

339 Tablets of VOTRIENT are for oral administration. Each 200 mg tablet of VOTRIENT  
340 contains 216.7 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base.  
341 Each 400 mg tablet of VOTRIENT contains 433.4 mg of pazopanib hydrochloride, equivalent to  
342 400 mg of pazopanib free base.

343 The inactive ingredients of VOTRIENT are: **Tablet Core:** Magnesium stearate,  
344 microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Gray film-coat (200 mg  
345 tablet): Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400),  
346 polysorbate 80, titanium dioxide. Yellow film-coat (400 mg tablet): Hypromellose, iron oxide  
347 yellow, macrogol/PEG 400, polysorbate 80, titanium dioxide.

348 **12 CLINICAL PHARMACOLOGY**

349 **12.1 Mechanism of Action**

350 Pazopanib is a multi- tyrosine kinase inhibitor of vascular endothelial growth factor  
351 receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)- $\alpha$   
352 and - $\beta$ , fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2  
353 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and  
354 transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited  
355 ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR- $\beta$  receptors. In vivo,  
356 pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in  
357 a mouse model, and the growth of some human tumor xenografts in mice.

358 **12.2 Pharmacodynamics**

359 Increases in blood pressure have been observed and are related to steady-state trough  
360 plasma pazopanib concentrations.

361 The QT prolongation potential of pazopanib was assessed as part of an uncontrolled.  
362 open-label, dose escalation study in advanced cancer patients. Sixty-three patients received doses  
363 of pazopanib ranging from 50 to 2,000 mg daily. Serial ECGs were collected on Day 1 and  
364 single pre-dose ECGs were collected on Days 8, 15, and 22 to evaluate the effect of pazopanib  
365 on QTc intervals. Two of the 63 patients had QTcF (corrected QT by the Fridericia method)  
366 >500 msec and three patients had an increase in QTcF >60 msec from baseline. [See Warnings  
367 and Precautions (5.2).]

368 **12.3 Pharmacokinetics**

369 Absorption: Pazopanib is absorbed orally with median time to achieve peak  
370 concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean  
371 AUC and  $C_{max}$  of 1,037 hr• $\mu$ g/mL and 58.1  $\mu$ g/mL (equivalent to 132  $\mu$ M), respectively. There  
372 was no consistent increase in AUC or  $C_{max}$  at pazopanib doses above 800 mg.

373 Administration of a single pazopanib 400 mg crushed tablet increased AUC<sub>(0-72)</sub> by 46%  
374 and  $C_{max}$  by approximately 2 fold and decreased  $t_{max}$  by approximately 2 hours compared to  
375 administration of the whole tablet. These results indicate that the bioavailability and the rate of  
376 pazopanib oral absorption are increased after administration of the crushed tablet relative to  
377 administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets  
378 of VOTRIENT should not be crushed.

379 Systemic exposure to pazopanib is increased when administered with food.  
380 Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold  
381 increase in AUC and  $C_{max}$ . Therefore, pazopanib should be administered at least 1 hour before or  
382 2 hours after a meal [see Dosage and Administration (2.1)].

383 Distribution: Binding of pazopanib to human plasma protein in vivo was greater than  
384 99% with no concentration dependence over the range of 10 to 100  $\mu$ g/mL. In vitro studies  
385 suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein  
386 (BCRP).

387 Metabolism: In vitro studies demonstrated that pazopanib is metabolized by CYP3A4  
388 with a minor contribution from CYP1A2 and CYP2C8.

389 Elimination: Pazopanib has a mean half-life of 30.9 hours after administration of the  
390 recommended dose of 800 mg. Elimination is primarily via feces with renal elimination  
391 accounting for <4% of the administered dose.

392 Hepatic Impairment: Interim data from a dose escalation study assessed the influence of  
393 hepatic impairment on the safety and pharmacokinetics of pazopanib in cancer patients with  
394 normal hepatic function and in patients with mild, moderate and severe hepatic impairment. The  
395 starting doses were 800, 400, 200, and 100 mg once daily for patients with normal hepatic  
396 function and patients with mild, moderate, and severe hepatic impairment, respectively.

397 Pharmacokinetic data from patients with normal hepatic function (n = 12) and moderate  
398 (n = 7) hepatic impairment indicate that pazopanib clearance was decreased by 50% in those  
399 with moderate hepatic impairment. The maximum tolerated pazopanib dose in patients with  
400 moderate hepatic impairment is 200 mg once daily. There are no data on patients with mild or  
401 severe hepatic impairment. [See *Use in Specific Populations (8.6).*]

402 Drug Interactions: Coadministration of oral pazopanib with CYP3A4 inhibitors has  
403 resulted in increased plasma pazopanib concentrations. Concurrent administration of a single  
404 dose of pazopanib eye drops with the strong CYP3A4 inhibitor and Pgp inhibitor, ketoconazole,  
405 in healthy volunteers resulted in 220% and 150% increase in mean AUC<sub>(0-t)</sub> and C<sub>max</sub> values,  
406 respectively. [See *Dosage and Administration (2.2) and Drug Interactions (7.1).*]

407 Administration of 1,500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp,  
408 and BCRP, with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean  
409 pazopanib AUC<sub>(0-24)</sub> and C<sub>max</sub> compared to administration of 800 mg pazopanib alone.

410 In vitro studies with human liver microsomes showed that pazopanib inhibited the  
411 activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction  
412 of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology  
413 studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a  
414 clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate),  
415 warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer  
416 patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and C<sub>max</sub> of  
417 midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of  
418 dextromethorphan to dextrophan concentrations in the urine after oral administration of  
419 dextromethorphan (CYP2D6 probe substrate). Coadministration of pazopanib 800 mg once daily  
420 and paclitaxel 80 mg/m<sup>2</sup> (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean  
421 increase of 26% and 31% in paclitaxel AUC and C<sub>max</sub>, respectively. [See *Drug Interactions*  
422 *(7.2).*]

423 In vitro studies also showed that pazopanib inhibits UGT1A1 and OATP1B1 with IC<sub>50</sub>s  
424 of 1.2 and 0.79 μM, respectively. Pazopanib may increase concentrations of drugs eliminated by  
425 UGT1A1 and OATP1B1.

426 **12.5 Pharmacogenomics**

427 Pazopanib can increase serum total bilirubin levels [*see Warnings and Precautions*  
428 (5.1)]. In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin  
429 for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA  
430 repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during  
431 pazopanib treatment. In this analysis, the (TA)<sup>7</sup>/(TA)<sup>7</sup> genotype (UGT1A1\*28/\*28) (underlying  
432 genetic susceptibility to Gilbert’s syndrome) was associated with a statistically significant  
433 increase in the incidence of hyperbilirubinemia relative to the (TA)<sup>6</sup>/(TA)<sup>6</sup> and (TA)<sup>6</sup>/(TA)<sup>7</sup>  
434 genotypes.

435 **13 NONCLINICAL TOXICOLOGY**

436 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

437 Carcinogenicity studies with pazopanib have not been conducted. However, in a 13-week  
438 study in mice, proliferative lesions in the liver including eosinophilic foci in 2 females and a  
439 single case of adenoma in another female was observed at doses of 1,000 mg/kg/day  
440 (approximately 2.5 times the human clinical exposure based on AUC).

441 Pazopanib did not induce mutations in the microbial mutagenesis (Ames) assay and was  
442 not clastogenic in both the in vitro cytogenetic assay using primary human lymphocytes and in  
443 the in vivo rat micronucleus assay.

444 Pazopanib may impair fertility in humans. In female rats, reduced fertility including  
445 increased pre-implantation loss and early resorptions were noted at dosages  $\geq 30$  mg/kg/day  
446 (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was  
447 seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC).  
448 Post-implantation loss, embryoletality, and decreased fetal body weight were noted in females  
449 administered doses  $\geq 10$  mg/kg/day (approximately 0.3 times the human clinical exposure based  
450 on AUC). Decreased corpora lutea and increased cysts were noted in mice given  
451  $\geq 100$  mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given  $\geq 300$  mg/kg/day for  
452 26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC,  
453 respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to  
454 34 weeks (approximately 0.4 times the human clinical exposure based on AUC).

455 Pazopanib did not affect mating or fertility in male rats. However, there were reductions  
456 in sperm production rates and testicular sperm concentrations at doses  $\geq 3$  mg/kg/day, epididymal  
457 sperm concentrations at doses  $\geq 30$  mg/kg/day, and sperm motility at  $\geq 100$  mg/kg/day following  
458 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and  
459 epididymal weights at doses of  $\geq 30$  mg/kg/day (approximately 0.35 times the human clinical  
460 exposure based on AUC); atrophy and degeneration of the testes with aspermia, hypospermia  
461 and cribiform change in the epididymis was also observed at this dose in the 6-month toxicity  
462 studies in male rats.

463 **14 CLINICAL STUDIES**

464 The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a  
465 randomized, double-blind, placebo-controlled, multicenter, Phase 3 study. Patients (N = 435)  
466 with locally advanced and/or metastatic RCC who had received either no prior therapy or one  
467 prior cytokine-based systemic therapy were randomized (2:1) to receive VOTRIENT 800 mg  
468 once daily or placebo once daily. The primary objective of the study was to evaluate and  
469 compare the 2 treatment arms for progression-free survival (PFS); the secondary endpoints  
470 included overall survival (OS), overall response rate (RR), and duration of response.

471 Of the total of 435 patients enrolled in this study, 233 patients had no prior systemic  
472 therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or INF $\alpha$ -based  
473 therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics  
474 were balanced between the VOTRIENT and placebo arms. The majority of patients were male  
475 (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were  
476 Asian and less than 1% were other. Forty-two percent were ECOG performance status 0 and  
477 58% were ECOG performance status 1. All patients had clear cell histology (90%) or  
478 predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more  
479 organs involved with metastatic disease. The most common metastatic sites at baseline were lung  
480 (74%), lymph nodes (56%), bone (27%), and liver (25%).

481 A similar proportion of patients in each arm were treatment-naïve and cytokine-  
482 pretreated (see Table 3). In the cytokine-pretreated subgroup, the majority (75%) had received  
483 interferon-based treatment. Similar proportions of patients in each arm had prior nephrectomy  
484 (89% and 88% for VOTRIENT and placebo, respectively).

485 The analysis of the primary endpoint PFS was based on disease assessment by  
486 independent radiological review in the entire study population. OS data were not mature at the  
487 time of the interim survival analysis. Efficacy results are presented in Table 3 and Figure 1.

488

489 **Table 3. Efficacy Results by Independent Assessment**

Endpoint/Study Population	VOTRIENT	Placebo	HR (95% CI)
<b>PFS</b>			
Overall ITT Median (months)	N = 290 9.2	N = 145 4.2	0.46 <sup>a</sup> (0.34, 0.62)
Treatment-naïve subgroup Median (months)	N = 155 (53%) 11.1	N = 78 (54%) 2.8	0.40 (0.27, 0.60)
Cytokine pre-treated subgroup Median (months)	N = 135 (47%) 7.4	N = 67 (46%) 4.2	0.54 (0.35, 0.84)
<b>Response Rate (CR + PR)</b> % (95% CI)	N = 290 30 (25.1, 35.6)	N = 145 3 (0.5, 6.4)	–
Duration of response Median (weeks) (95% CI)	58.7 (52.1, 68.1)	– <sup>b</sup>	

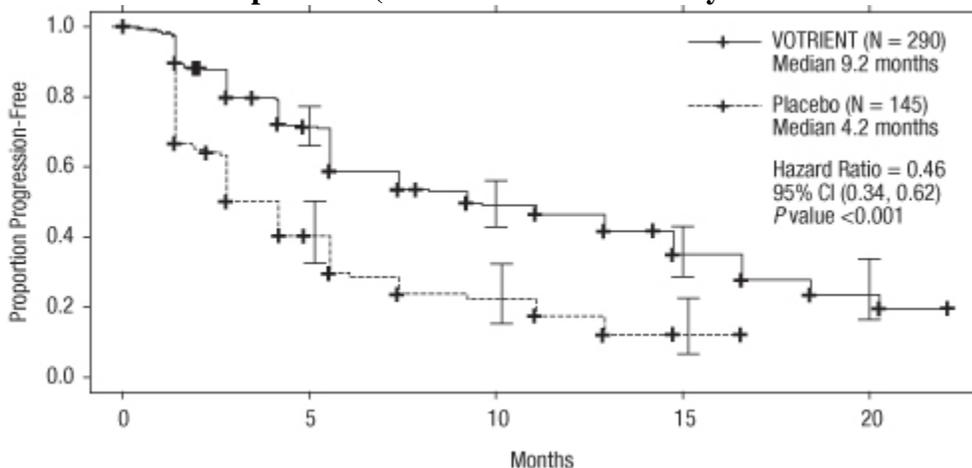
490 HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival; CR = Complete  
491 Response; PR = Partial Response

492 <sup>a</sup> P value <0.001

493 <sup>b</sup> There were only 5 objective responses.

494

495 **Figure 1. Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment**  
496 **for the Overall Population (Treatment-Naïve and Cytokine Pre-Treated Populations)**



497

498

499 **16 HOW SUPPLIED/STORAGE AND HANDLING**

500 The 200 mg tablets of VOTRIENT are modified capsule-shaped, gray, film-coated with  
501 GS JT debossed on one side and are available in:

502 Bottles of 30 tablets: NDC 0173-0804-13  
503 Bottles of 90 tablets: NDC 0173-0804-59  
504 Bottles of 120 tablets: NDC 0173-0804-09  
505 The 400 mg tablets of VOTRIENT are modified capsule-shaped, yellow, film-coated  
506 with GS UHL debossed on one side and are available in:  
507 Bottles of 30 tablets: NDC 0173-0805-13  
508 Bottles of 60 tablets: NDC 0173-0805-18  
509 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP  
510 Controlled Room Temperature].

## 511 **17 PATIENT COUNSELING INFORMATION**

512 See Medication Guide. The Medication Guide is contained in a separate leaflet that  
513 accompanies the product. However, inform patients of the following:

- 514 • Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor  
515 serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least  
516 once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform  
517 patients that they should report any of the following signs and symptoms of liver problems to  
518 their healthcare provider right away.
  - 519 • yellowing of the skin or the whites of the eyes (jaundice),
  - 520 • unusual darkening of the urine,
  - 521 • unusual tiredness,
  - 522 • right upper stomach area pain.
- 523 • Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported  
524 with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their  
525 healthcare provider if moderate to severe diarrhea occurs.
- 526 • Women of childbearing potential should be advised of the potential hazard to the fetus and to  
527 avoid becoming pregnant.
- 528 • Patients should be advised to inform their healthcare providers of all concomitant  
529 medications, vitamins, or dietary and herbal supplements.
- 530 • Patients should be advised that depigmentation of the hair or skin may occur during treatment  
531 with VOTRIENT.
- 532 • Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours  
533 after a meal).

534  
535 VOTRIENT is a trademark of GlaxoSmithKline.  
536



537  
538 GlaxoSmithKline

539 Research Triangle Park, NC 27709  
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## MEDICATION GUIDE

### VOTRIENT™ (VO-tree-ent) (pazopanib) Tablets

Read the Medication Guide that comes with VOTRIENT before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

#### **What is the most important information I should know about VOTRIENT?**

- **VOTRIENT can cause serious liver problems including death.** Your healthcare provider will do blood tests to check your liver before you start and while you take VOTRIENT.

#### **Tell your healthcare provider right away if you have any of these signs of liver problems:**

- yellowing of your skin or the whites of your eyes (jaundice)
- dark urine
- tiredness
- nausea or vomiting
- loss of appetite
- pain on the right side of your stomach
- bruise easily

#### **What is VOTRIENT?**

VOTRIENT is a prescription medicine used to treat advanced renal cell cancer in adults. It is not known if VOTRIENT is safe or effective in children under 18 years of age.

#### **What should I tell my healthcare provider before taking VOTRIENT?**

##### **Before you take VOTRIENT, tell your healthcare provider if you:**

- have or had liver problems
- have high blood pressure
- have heart problems or an irregular heartbeat including QT prolongation
- have a history of a stroke
- have coughed up blood in the last 6 months
- had bleeding of your stomach or intestines in the last 6 months
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two parts of your gastrointestinal tract (fistula)
- have thyroid problems
- had recent surgery (within the last 7 days) or are going to have surgery
- have any other medical conditions
- are pregnant or plan to become pregnant. VOTRIENT can harm your unborn baby. You should not become pregnant while you are taking VOTRIENT.

- 582 • are breast-feeding or plan to breast-feed. It is not known if VOTRIENT passes into your  
583 breast milk. You and your healthcare provider should decide if you will take VOTRIENT or  
584 breast-feed. You should not do both.  
585

586 **Tell your healthcare provider about all the medicines you take** including prescription and  
587 non-prescription medicines, vitamins, and herbal supplements. VOTRIENT may affect the way  
588 other medicines work and other medicines may affect how VOTRIENT works.  
589

590 **Especially, tell your healthcare provider if you:**

- 591 • take medicines that can affect enzyme metabolism such as:
- 592 • some antibiotics (used to treat infections)
  - 593 • some drugs used to treat HIV
  - 594 • some drugs used to treat depression
  - 595 • drugs used to treat irregular heart beats
- 596 • drink grapefruit juice

597  
598 Ask your healthcare provider if you are not sure if your medicine is one that is listed above.  
599

600 Know the medicines you take. Keep a list of them and show it to your healthcare provider and  
601 pharmacist when you get a new medicine.  
602

603 **How should I take VOTRIENT?**

- 604 • Take VOTRIENT exactly as your healthcare provider tells you. Your healthcare provider  
605 will tell you how much VOTRIENT to take.
- 606 • Your healthcare provider may change your dose.
- 607 • Take VOTRIENT on an empty stomach, at least 1 hour before or 2 hours after food.
- 608 • Do not crush tablets of VOTRIENT.
- 609 • Do not eat grapefruit or drink grapefruit juice at the same time as tablets of VOTRIENT.  
610 They may change the amount of VOTRIENT in your body.
- 611 • If you miss a dose, take it as soon as you remember. Do not take it if it is close (within  
612 12 hours) to your next dose. Just take the next dose at your regular time. Do not take more  
613 than 1 dose of VOTRIENT at a time.
- 614 • Your healthcare provider will test your blood and heart before you start and while you take  
615 VOTRIENT.  
616

617 **What are the possible side effects of VOTRIENT?**

618 **VOTRIENT may cause serious side effects including:**  
619

- 620 • See “**What is the most important information I should know about VOTRIENT?**”.
- 621 • **high blood pressure**

- 622 • **irregular or fast heartbeat or fainting**
- 623 • **heart attack or stroke:** chest pain or pressure, pain in your arms, back, neck or jaw,
- 624 shortness of breath, numbness or weakness on one side of your body, trouble talking,
- 625 headache, or dizziness.
- 626 • **bleeding problems:** unusual bleeding, bruising, wounds that do not heal.
- 627 • **tear in your stomach or intestinal wall (perforation) or bleeding:** pain, swelling in your
- 628 stomach-area, vomiting blood, and black sticky stools.
- 629 • **thyroid problems**

630

631 **Call your healthcare provider right away, if you have any of the symptoms listed above.**

632

633 The most common side effects of VOTRIENT include:

- 634 • diarrhea
- 635 • change in hair color
- 636 • nausea or vomiting
- 637 • loss of appetite
- 638 • feeling tired

639

640

641 Tell your healthcare provider if you have any side effect that bothers you or that does not go  
642 away. These are not all the possible side effects of VOTRIENT. For more information, ask your  
643 healthcare provider or pharmacist.

644

645 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
646 800-FDA-1088.

647

#### 648 **How should I store VOTRIENT Tablets?**

649 Store VOTRIENT between 59°F to 86°F (15°C to 30°C).

650

651 **Keep VOTRIENT and all medicines out of the reach of children.**

652

#### 653 **General information about the safe and effective use of VOTRIENT:**

654 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
655 Do not use VOTRIENT for a condition for which it was not prescribed. Do not give VOTRIENT  
656 to other people even if they have the same symptoms that you have. It may harm them.

657

658 This Medication Guide summarizes the most important information about VOTRIENT. If you  
659 would like more information, talk with your healthcare provider. You can ask your pharmacist or  
660 healthcare provider for information about VOTRIENT that is written for healthcare  
661 professionals. For more information, go to [www.VOTRIENT.com](http://www.VOTRIENT.com) or call 1-888-825-5249.

662

663 **What are the ingredients in VOTRIENT?**

664 **Active Ingredient:** pazopanib.

665 **Inactive Ingredients:** hypromellose, iron oxide black (200 mg tablet), iron oxide yellow  
666 (400 mg tablet), macrogol/ polyethylene glycol 400 (PEG 400), magnesium stearate,  
667 microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate, titanium dioxide.

668

669 VOTRIENT is a registered trademark of GlaxoSmithKline.

670

671 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

672



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674 GlaxoSmithKline

675 Research Triangle Park, NC 27709

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679 Revised: October 2009

680 VTR:xMG