

## 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 trials.

Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended [see Warnings and Precautions (5.1)].

### RECENT MAJOR CHANGES

|   |         |
|---|---------|
| Indications and Usage (1)                     | 04/2012 |
| Dosage and Administration (2.2)               | 04/2012 |
| Warnings and Precautions (5.1-5.9, 5.11-5.14) | 04/2012 |

### INDICATIONS AND USAGE

VOTRIENT is a kinase inhibitor indicated for the treatment of patients with:

- advanced renal cell carcinoma. (1)
- advanced soft tissue sarcoma who have received prior chemotherapy. (1)

Limitations of Use:

The efficacy of VOTRIENT for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors has not been demonstrated.

### 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 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)
- Cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction have occurred. Monitor blood pressure and manage hypertension promptly. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction. (5.3)
- 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. (5.4)
- Arterial thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for these events. (5.5)

- Venous thrombotic events (VTE) have been observed, including fatal pulmonary emboli (PE). Monitor for signs and symptoms of VTE and PE. (5.6)
- Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. (5.7)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. Permanently discontinue VOTRIENT if signs or symptoms of RPLS occur. (5.8)
- Hypertension including hypertensive crisis has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor blood pressure within one week after starting VOTRIENT and frequently thereafter. (5.9)
- Interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. (5.10)
- Hypothyroidism may occur. Monitoring of thyroid function tests is recommended. (5.11)
- Proteinuria: Monitor urine protein. Interrupt treatment for 24-hour urine protein  $\geq 3$  grams and discontinue for repeat episodes despite dose reductions. (5.12)
- Infection: Serious infections (with or without neutropenia), some with fatal outcome, have been reported. Monitor for signs and symptoms and treat active infection promptly. Consider discontinuation of VOTRIENT. (5.13)
- 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. (5.15, 8.1)

### ADVERSE REACTIONS

The most common adverse reactions in patients with advanced renal cell carcinoma ( $\geq 20\%$ ) are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. (6.1)

The most common adverse reactions in patients with advanced soft tissue sarcoma ( $\geq 20\%$ ) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea and skin hypopigmentation. (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. Reduce the dose 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)
- Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2012

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: HEPATOTOXICITY**

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

## 6 **1 INDICATIONS AND USAGE**

7 VOTRIENT<sup>®</sup> is indicated for the treatment of patients with advanced renal cell  
8 carcinoma (RCC).

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

### 11 **Limitation of Use:**

12 The efficacy of VOTRIENT for the treatment of patients with adipocytic STS or  
13 gastrointestinal stromal tumors has not been demonstrated.

## 14 **2 DOSAGE AND ADMINISTRATION**

### 15 **2.1 Recommended Dosing**

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

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

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

### 22 **2.2 Dose Modification Guidelines**

23 In RCC, the initial dose reduction should be 400 mg, and additional dose decrease or  
24 increase should be in 200 mg steps based on individual tolerability.

25 In STS, a decrease or increase should be in 200 mg steps based on individual tolerability.

26 **Hepatic Impairment:** No dose adjustment is required in patients with mild hepatic  
27 impairment. In patients with moderate hepatic impairment, alternatives to VOTRIENT should be  
28 considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should  
29 be reduced to 200 mg per day. VOTRIENT is not recommended in patients with severe hepatic  
30 impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

31 **Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4  
32 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and  
33 should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the  
34 dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur  
35 during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed

36 without inhibitors. However, there are no clinical data with this dose adjustment in patients  
37 receiving strong CYP3A4 inhibitors [see *Drug Interactions (7.1)*].

38 **Concomitant Strong CYP3A4 Inducer:** The concomitant use of strong CYP3A4  
39 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided.  
40 VOTRIENT should not be used in patients who cannot avoid chronic use of strong CYP3A4  
41 inducers [see *Drug Interactions (7.1)*].

### 42 **3 DOSAGE FORMS AND STRENGTHS**

43 200 mg tablets of VOTRIENT — modified capsule-shaped, gray, film-coated with GS JT  
44 debossed on one side. Each tablet contains 216.7 mg of pazopanib hydrochloride equivalent to  
45 200 mg of pazopanib.

### 46 **4 CONTRAINDICATIONS**

47 None.

### 48 **5 WARNINGS AND PRECAUTIONS**

#### 49 **5.1 Hepatic Toxicity and Hepatic Impairment**

50 In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum  
51 transaminases (ALT, AST) and bilirubin, was observed. This hepatotoxicity can be severe and  
52 fatal. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase  
53 elevations of any grade occurred in the first 18 weeks) [see *Dosage and Administration (2.2)*].

54 In the randomized RCC trial, ALT >3 X ULN was reported in 18% and 3% of the  
55 VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients  
56 who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in  
57 ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X  
58 ULN occurred in 2% (5/290) of patients on VOTRIENT and 1% (2/145) on placebo.

59 In the randomized STS trial, ALT >3 X ULN was reported in 18% and 5% of the  
60 VOTRIENT and placebo groups, respectively. ALT >8 X ULN was reported in 5% and 2% of  
61 the VOTRIENT and placebo groups, respectively. Concurrent elevation in ALT >3 X ULN and  
62 bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in  
63 2% (4/240) of patients on VOTRIENT and <1% (1/123) on placebo.

64 Two-tenths percent of the patients (2/977) from trials that supported the RCC indication  
65 died with disease progression and hepatic failure and 0.4% of patients (1/240) in the randomized  
66 STS trial died of hepatic failure.

- 67
- 68 • Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once  
69 every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic  
70 monitoring should then continue after this time period.
  - 71 • Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on  
72 VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or  
baseline.

- 73 • Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted  
74 until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with  
75 VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce  
76 VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver  
77 tests weekly for 8 weeks [see *Dosage and Administration (2.2)*]. Following reintroduction of  
78 VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently  
79 discontinued.
- 80 • If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN,  
81 VOTRIENT should be permanently discontinued. Patients should be monitored until  
82 resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated)  
83 hyperbilirubinemia may occur in patients with Gilbert's syndrome [see *Clinical*  
84 *Pharmacology (12.5)*]. Patients with only a mild indirect hyperbilirubinemia, known  
85 Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the  
86 recommendations outlined for isolated ALT elevations.

87 Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and  
88 should be undertaken with caution and close monitoring [see *Drug Interactions (7.3)*].  
89 Insufficient data are available to assess the risk of concomitant administration of alternative  
90 statins and VOTRIENT.

91 In patients with pre-existing moderate hepatic impairment, the starting dose of  
92 VOTRIENT should be reduced or alternatives to VOTRIENT should be considered. Treatment  
93 with VOTRIENT is not recommended in patients with pre-existing severe hepatic impairment,  
94 defined as total bilirubin >3 X ULN with any level of ALT [see *Dosage and Administration*  
95 *(2.2)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

## 96 **5.2 QT Prolongation and Torsades de Pointes**

97 In the RCC trials of VOTRIENT, QT prolongation ( $\geq 500$  msec) was identified on routine  
98 electrocardiogram monitoring in 2% (11/558) of patients. Torsades de pointes occurred in <1%  
99 (2/977) of patients who received VOTRIENT in the monotherapy trials.

100 In the randomized RCC and STS trials, 1% (3/290) of patients and 0.2% (1/240) of  
101 patients respectively, who received VOTRIENT had post-baseline values between 500 to 549  
102 msec. Post-baseline QT data were only collected in the STS trial if ECG abnormalities were  
103 reported as an adverse reaction. None of the 268 patients who received placebo on the two trials  
104 had post-baseline QTc values  $\geq 500$  msec.

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

## 110 **5.3 Cardiac Dysfunction**

111 In clinical trials with VOTRIENT, events of cardiac dysfunction such as decreased left  
112 ventricular ejection fraction (LVEF) and congestive heart failure have occurred. In the overall

113 safety population for RCC (N = 586), cardiac dysfunction was observed in 0.6% (4/586) of  
114 patients without routine on-study LVEF monitoring. In the randomized STS trial, myocardial  
115 dysfunction was defined as symptoms of cardiac dysfunction or  $\geq 15\%$  absolute decline in LVEF  
116 compared to baseline or a decline in LVEF of  $\geq 10\%$  compared to baseline that is also below the  
117 lower limit of normal. In patients who had baseline and follow up LVEF measurements,  
118 myocardial dysfunction occurred in 11% (16/142) of patients on VOTRIENT compared to 5%  
119 (2/40) of patients on placebo. One percent (3/240) of patients on VOTRIENT in the STS trial  
120 had congestive heart failure which did not resolve in one patient.

121 Fourteen of the 16 patients with myocardial dysfunction treated with VOTRIENT in the  
122 STS trial had concurrent hypertension which may have exacerbated cardiac dysfunction in  
123 patients at risk (e.g., those with prior anthracycline therapy) possibly by increasing cardiac  
124 afterload. Blood pressure should be monitored and managed promptly using a combination of  
125 anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at  
126 a reduced dose based on clinical judgment) [*see Warnings and Precautions (5.9)*]. Patients  
127 should be carefully monitored for clinical signs or symptoms of congestive heart failure.  
128 Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac  
129 dysfunction including previous anthracycline exposure.

#### 130 **5.4 Hemorrhagic Events**

131 Fatal hemorrhage occurred in 0.9% (5/586) in the RCC trials; there were no reports of  
132 fatal hemorrhage in the STS trials. In the randomized RCC trial, 13% (37/290) of patients treated  
133 with VOTRIENT and 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic  
134 event. The most common hemorrhagic events in the patients treated with VOTRIENT were  
135 hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine of 37  
136 patients treated with VOTRIENT who had hemorrhagic events experienced serious events  
137 including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of  
138 patients treated with VOTRIENT died from hemorrhage compared with no (0/145) patients on  
139 placebo. In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was  
140 observed in  $< 1\%$  (2/586) of patients treated with VOTRIENT.

141 In the randomized STS trial, 22% (53/240) of patients treated with VOTRIENT  
142 compared to 8% (10/123) treated with placebo experienced at least 1 hemorrhagic event. The  
143 most common hemorrhagic events were epistaxis (8%), mouth hemorrhage (3%), and anal  
144 hemorrhage (2%). Grade 4 hemorrhagic events in the STS population occurred in 1% (3/240)  
145 patients and included intracranial hemorrhage, subarachnoid hemorrhage and peritoneal  
146 hemorrhage.

147 VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral,  
148 or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used  
149 in those patients.

#### 150 **5.5 Arterial Thrombotic Events**

151 Fatal arterial thromboembolic events were observed in 0.3% (2/586) of patients in the  
152 RCC trials and in no patients in the STS trials. In the randomized RCC trial, 2% (5/290) of

153 patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had  
154 a cerebrovascular accident and 1% (4/290) had an event of transient ischemic attack. In the  
155 randomized STS trial, 2% (4/240) of patients receiving VOTRIENT experienced a myocardial  
156 infarction or ischemia, 0.4% (1/240) had a cerebrovascular accident and there were no incidents  
157 of transient ischemic attack. No arterial thrombotic events were reported in patients who received  
158 placebo in either trial. VOTRIENT should be used with caution in patients who are at increased  
159 risk for these events or who have had a history of these events. VOTRIENT has not been studied  
160 in patients who have had an arterial thrombotic event within the previous 6 months and should  
161 not be used in those patients.

## 162 **5.6 Venous Thromboembolic Events**

163 In RCC and STS trials of VOTRIENT, venous thromboembolic events including venous  
164 thrombosis and fatal pulmonary embolus have occurred. In the randomized STS trial, venous  
165 thromboembolic events were reported in 5% of patients treated with VOTRIENT compared to  
166 2% with placebo. In the randomized RCC trial, the rate was 1% in both arms. Fatal pulmonary  
167 embolus occurred in 1% (2/240) of STS patients receiving VOTRIENT and in no patients  
168 receiving placebo. There were no fatal pulmonary emboli in the RCC trial. Monitor for signs and  
169 symptoms of VTE and PE.

## 170 **5.7 Gastrointestinal Perforation and Fistula**

171 In the RCC and STS trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586)  
172 of patients and 1% (4/382) of patients receiving VOTRIENT, respectively. Fatal perforations  
173 occurred in 0.3% (2/586) of these patients in the RCC trials and in 0.3% (1/382) of these patients  
174 in the STS trials. Monitor for signs and symptoms of gastrointestinal perforation or fistula.

## 175 **5.8 Reversible Posterior Leukoencephalopathy Syndrome**

176 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in  
177 patients receiving VOTRIENT and may be fatal.

178 RPLS is a neurological disorder which can present with headache, seizure, lethargy,  
179 confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension  
180 may be present. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging.  
181 Discontinue VOTRIENT in patients developing RPLS.

## 182 **5.9 Hypertension**

183 Hypertension (systolic blood pressure  $\geq 150$  or diastolic blood pressure  $\geq 100$  mm Hg) and  
184 hypertensive crisis were observed in patients treated with VOTRIENT. Blood pressure should be  
185 well-controlled prior to initiating VOTRIENT. Hypertension occurs early in the course of  
186 treatment (40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks).  
187 Blood pressure should be monitored early after starting treatment (no longer than one week) and  
188 frequently thereafter to ensure blood pressure control. Approximately 40% of patients who  
189 received VOTRIENT experienced hypertension. Grade 3 hypertension was reported in 4% to 7%  
190 of patients receiving VOTRIENT [*see Adverse Reactions (6.1)*].

191 Increased blood pressure should be treated promptly with standard anti-hypertensive  
192 therapy and dose reduction or interruption of VOTRIENT as clinically warranted. VOTRIENT

193 should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and  
194 persistent despite anti-hypertensive therapy and dose reduction. Approximately 1% of patients  
195 required permanent discontinuation of VOTRIENT because of hypertension [*see Dosage and*  
196 *Administration (2.2)*].

### 197 **5.10 Wound Healing**

198 No formal trials on the effect of VOTRIENT on wound healing have been conducted.  
199 Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may  
200 impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to  
201 scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical  
202 judgment of adequate wound healing. VOTRIENT should be discontinued in patients with  
203 wound dehiscence.

### 204 **5.11 Hypothyroidism**

205 Hypothyroidism, confirmed based on a simultaneous rise of TSH and decline of T4, was  
206 reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial and in  
207 5% (11/240) of patients treated with VOTRIENT in the randomized STS trial. No patients on the  
208 placebo arm of either trial had hypothyroidism. In RCC and STS trials of VOTRIENT,  
209 hypothyroidism was reported as an adverse reaction in 4% (26/586) and 5% (20/382) of patients,  
210 respectively. Proactive monitoring of thyroid function tests is recommended.

### 211 **5.12 Proteinuria**

212 In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9%  
213 (27/290) of patients receiving VOTRIENT and in no patients receiving placebo. In 2 patients,  
214 proteinuria led to discontinuation of treatment with VOTRIENT. In the randomized STS trial,  
215 proteinuria was reported as an adverse reaction in 1% (2/240) of patients, and nephrotic  
216 syndrome was reported in 1 patient, treated with VOTRIENT compared to none in patients  
217 receiving placebo. Treatment was withdrawn in the patient with nephrotic syndrome.

218 Baseline and periodic urinalysis during treatment is recommended with follow up  
219 measurement of 24-hour urine protein as clinically indicated. Interrupt VOTRIENT and dose  
220 reduce for 24-hour urine protein  $\geq 3$  grams; discontinue VOTRIENT for repeat episodes despite  
221 dose reductions [*see Dosage and Administration (2.2)*].

### 222 **5.13 Infection**

223 Serious infections (with or without neutropenia), including some with fatal outcome,  
224 have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate  
225 anti-infective therapy promptly and consider interruption or discontinuation of VOTRIENT for  
226 serious infections.

### 227 **5.14 Increased Toxicity with Other Cancer Therapy**

228 VOTRIENT is not indicated for use in combination with other agents. Clinical trials of  
229 VOTRIENT in combination with pemetrexed and lapatinib were terminated early due to  
230 concerns over increased toxicity and mortality. The fatal toxicities observed included pulmonary  
231 hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination  
232 dose has not been established with these regimens.

233 **5.15 Pregnancy**

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

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

243 **6 ADVERSE REACTIONS**

244 **6.1 Clinical Trials Experience**

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

248 Potentially serious adverse reactions with VOTRIENT included:

- 249 • Hepatotoxicity [*see Warnings and Precautions (5.1)*]
- 250 • QT prolongation and torsades de pointes [*see Warnings and Precautions (5.2)*]
- 251 • Cardiac dysfunction [*see Warnings and Precautions (5.3)*]
- 252 • Hemorrhagic events [*see Warnings and Precautions (5.4)*]
- 253 • Arterial and venous thrombotic events [*see Warnings and Precautions (5.5 and 5.6)*]
- 254 • Gastrointestinal perforation and fistula [*see Warnings and Precautions (5.7)*]
- 255 • Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [*see Warnings and*  
256 *Precautions (5.8)*]
- 257 • Hypertension [*see Warnings and Precautions (5.9)*]
- 258 • Infection [*see Warnings and Precautions (5.13)*]
- 259 • Increased toxicity with other cancer therapies [*see Warnings and Precautions (5.14)*]

260 **Renal Cell Carcinoma:** The safety of VOTRIENT has been evaluated in 977 patients in  
261 the monotherapy trials which included 586 patients with RCC at the time of NDA submission.  
262 With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly  
263 observed adverse reactions ( $\geq 20\%$ ) in the 586 patients were diarrhea, hypertension, hair color  
264 change, nausea, fatigue, anorexia, and vomiting.

265 The data described below reflect the safety profile of VOTRIENT in 290 RCC patients  
266 who participated in a randomized, double-blind, placebo-controlled trial [*see Clinical Studies*  
267 *(14.1)*]. The median duration of treatment was 7.4 months (range 0 to 23) for patients who  
268 received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent of  
269 patients on VOTRIENT required a dose interruption. Thirty-six percent of patients on  
270 VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring  
271 in  $\geq 10\%$  of patients who received VOTRIENT.

272

273 **Table 1. Adverse Reactions Occurring in  $\geq 10\%$  of Patients with RCC who Received**  
274 **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       |

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

276

277 Other adverse reactions observed more commonly in patients treated with VOTRIENT  
278 than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain  
279 (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%),  
280 dysphonia (4% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia  
281 (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin  
282 depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

283 Table 2 presents the most common laboratory abnormalities occurring in >10% of  
284 patients who received VOTRIENT and more commonly ( $\geq 5\%$ ) in patients who received  
285 VOTRIENT versus placebo.

286

287 **Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients with RCC who**  
 288 **Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT**  
 289 **Versus Placebo**

| Parameters                | VOTRIENT<br>(N = 290)   |         |         | Placebo<br>(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       |

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 291

292 **Soft Tissue Sarcoma:** The safety of VOTRIENT has been evaluated in 382 patients  
 293 with advanced soft tissue sarcoma, with a median duration of treatment of 3.6 months (range 0 to  
 294 53). The most commonly observed adverse reactions (≥20%) in the 382 patients were fatigue,  
 295 diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair  
 296 color changes, musculoskeletal pain, headache, dysgeusia, dyspnea and skin hypopigmentation.

297 The data described below reflect the safety profile of VOTRIENT in 240 patients who  
 298 participated in a randomized, double-blind, placebo-controlled trial [*see Clinical Studies (14.2)*].  
 299 The median duration of treatment was 4.5 months (range 0 to 24) for patients who received  
 300 VOTRIENT and 1.9 months (range 0 to 24) for the placebo arm. Fifty-eight percent of patients  
 301 on VOTRIENT required a dose interruption. Thirty-eight percent of patients on VOTRIENT had  
 302 their dose reduced. Fourteen percent of patients who received VOTRIENT discontinued therapy  
 303 due to adverse reactions. Table 3 presents the most common adverse reactions occurring in  
 304 ≥10% of patients who received VOTRIENT.  
 305

306 **Table 3. Adverse Reactions Occurring in  $\geq 10\%$  of Patients with STS who Received**  
307 **VOTRIENT**

| Adverse Reactions          | VOTRIENT<br>(N = 240)   |         |         | Placebo<br>(N = 123)    |         |         |
|----------------------------|-------------------------|---------|---------|-------------------------|---------|---------|
|                            | All Grades <sup>a</sup> | Grade 3 | Grade 4 | All Grades <sup>a</sup> | Grade 3 | Grade 4 |
|                            | %                       | %       | %       | %                       | %       | %       |
| Fatigue                    | 65                      | 13      | 1       | 48                      | 4       | 1       |
| Diarrhea                   | 59                      | 5       | 0       | 15                      | 1       | 0       |
| Nausea                     | 56                      | 3       | 0       | 22                      | 2       | 0       |
| Weight decreased           | 48                      | 4       | 0       | 15                      | 0       | 0       |
| Hypertension               | 42                      | 7       | 0       | 6                       | 0       | 0       |
| Appetite decreased         | 40                      | 6       | 0       | 19                      | 0       | 0       |
| Hair color changes         | 39                      | 0       | 0       | 2                       | 0       | 0       |
| Vomiting                   | 33                      | 3       | 0       | 11                      | 1       | 0       |
| Tumor pain                 | 29                      | 8       | 0       | 21                      | 7       | 2       |
| Dysgeusia                  | 28                      | 0       | 0       | 3                       | 0       | 0       |
| Headache                   | 23                      | 1       | 0       | 8                       | 0       | 0       |
| Musculoskeletal pain       | 23                      | 2       | 0       | 20                      | 2       | 0       |
| Myalgia                    | 23                      | 2       | 0       | 9                       | 0       | 0       |
| Gastrointestinal pain      | 23                      | 3       | 0       | 9                       | 4       | 0       |
| Dyspnea                    | 20                      | 5       | <1      | 17                      | 5       | 1       |
| Exfoliative rash           | 18                      | <1      | 0       | 9                       | 0       | 0       |
| Cough                      | 17                      | <1      | 0       | 12                      | <1      | 0       |
| Peripheral edema           | 14                      | 2       | 0       | 9                       | 2       | 0       |
| Mucositis                  | 12                      | 2       | 0       | 2                       | 0       | 0       |
| Alopecia                   | 12                      | 0       | 0       | 1                       | 0       | 0       |
| Dizziness                  | 11                      | 1       | 0       | 4                       | 0       | 0       |
| Skin disorder <sup>b</sup> | 11                      | 2       | 0       | 1                       | 0       | 0       |
| Skin hypopigmentation      | 11                      | 0       | 0       | 0                       | 0       | 0       |
| Stomatitis                 | 11                      | <1      | 0       | 3                       | 0       | 0       |
| Chest pain                 | 10                      | 2       | 0       | 6                       | 0       | 0       |

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

309 <sup>b</sup> 27 of the 28 cases of skin disorder were palmar-plantar erythrodysesthesia.

310

311 Other adverse reactions observed more commonly in patients treated with VOTRIENT  
312 that occurred in  $\geq 5\%$  of patients and at an incidence of more than 2% difference from placebo  
313 included insomnia (9% versus 6%), hypothyroidism (8% versus 0), dysphonia (8% versus 2%),  
314 epistaxis (8% versus 2%), left ventricular dysfunction (8% versus 4%), dyspepsia (7% versus

315 2%), dry skin (6% versus <1%), chills (5% versus 1%), vision blurred (5% versus 2%), nail  
316 disorder (5% versus 0%).

317 Table 4 presents the most common laboratory abnormalities occurring in >10% of  
318 patients who received VOTRIENT and more commonly (≥5%) in patients who received  
319 VOTRIENT versus placebo.

320

321 **Table 4. Selected Laboratory Abnormalities Occurring in >10% of Patients with STS who**  
322 **Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT**  
323 **Versus Placebo**

| Parameters                        | VOTRIENT<br>(N = 240)      |         |         | Placebo<br>(N = 123)       |         |         |
|-----------------------------------|----------------------------|---------|---------|----------------------------|---------|---------|
|                                   | All<br>Grades <sup>a</sup> | Grade 3 | Grade 4 | All<br>Grades <sup>a</sup> | Grade 3 | Grade 4 |
|                                   | %                          | %       | %       | %                          | %       | %       |
| <b>Hematologic</b>                |                            |         |         |                            |         |         |
| Leukopenia                        | 44                         | 1       | 0       | 15                         | 0       | 0       |
| Lymphocytopenia                   | 43                         | 10      | 0       | 36                         | 9       | 2       |
| Thrombocytopenia                  | 36                         | 3       | 1       | 6                          | 0       | 0       |
| Neutropenia                       | 33                         | 4       | 0       | 7                          | 0       | 0       |
| <b>Chemistry</b>                  |                            |         |         |                            |         |         |
| AST increased                     | 51                         | 5       | 3       | 22                         | 2       | 0       |
| ALT increased                     | 46                         | 8       | 2       | 18                         | 2       | 1       |
| Glucose increased                 | 45                         | <1      | 0       | 35                         | 2       | 0       |
| Albumin decreased                 | 34                         | 1       | 0       | 21                         | 0       | 0       |
| Alkaline phosphatase<br>increased | 32                         | 3       | 0       | 23                         | 1       | 0       |
| Sodium decreased                  | 31                         | 4       | 0       | 20                         | 3       | 0       |
| Total bilirubin increased         | 29                         | 1       | 0       | 7                          | 2       | 0       |
| Potassium increased               | 16                         | 1       | 0       | 11                         | 0       | 0       |

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

325

326 **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in  
327 severity in both the RCC and STS clinical trials. Patients should be advised how to manage mild  
328 diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so  
329 appropriate management can be implemented to minimize its impact.

330 **Lipase Elevations:** In a single-arm RCC trial, increases in lipase values were observed  
331 for 27% (48/181) of patients. Elevations in lipase as an adverse reaction were reported for 4%  
332 (10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the RCC trials  
333 of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients.

334 Pneumothorax: Two of 290 patients treated with VOTRIENT and no patient on the  
335 placebo arm in the randomized RCC trial developed a pneumothorax. In the randomized trial of  
336 VOTRIENT for the treatment of STS, pneumothorax occurred in 3% (8/240) of patients treated  
337 with VOTRIENT and in no patients on the placebo arm.

## 338 **6.2 Postmarketing Experience**

339 The following adverse reactions have been identified during post approval use of  
340 VOTRIENT. Because these reactions are reported voluntarily from a population of uncertain size  
341 it is not always possible to reliably estimate the frequency or establish a causal relationship to  
342 drug exposure.

343 Reversible Posterior Leukoencephalopathy Syndrome [*see Warnings and Precautions*  
344 (5.8)]

## 345 **7 DRUG INTERACTIONS**

### 346 **7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

350 CYP3A4 Inhibitors: Coadministration of pazopanib with strong inhibitors of CYP3A4  
351 (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be  
352 avoided. Reduce the dose of VOTRIENT when it must be coadministered with strong CYP3A4  
353 inhibitors [*see Dosage and Administration (2.2)*]. Grapefruit juice should be avoided as it  
354 inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

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

### 358 **7.2 Effects of Pazopanib on CYP Substrates**

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

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

### 366 **7.3 Effect of Concomitant use of VOTRIENT and Simvastatin**

367 Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT  
368 elevations. Across monotherapy studies with VOTRIENT, ALT >3 X ULN was reported in  
369 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who  
370 had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT  
371 elevations, follow dosing guidelines for VOTRIENT or consider alternatives to VOTRIENT [*see*  
372 *Warnings and Precautions (5.1)*]. Alternatively, consider discontinuing simvastatin [*see*

373 *Warnings and Precautions (5.1)*]. Insufficient data are available to assess the risk of concomitant  
374 administration of alternative statins and VOTRIENT.

## 375 **8 USE IN SPECIFIC POPULATIONS**

### 376 **8.1 Pregnancy**

377 Pregnancy Category D [*see Warnings and Precautions (5.15)*].

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

380 In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic,  
381 fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis  
382 at a dose level of  $\geq 3$  mg/kg/day (approximately 0.1 times the human clinical exposure based on  
383 AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal  
384 subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or  
385 absent ossification. In addition, there was reduced fetal body weight, and pre- and post-  
386 implantation embryoletality in rats administered pazopanib at doses  $\geq 3$  mg/kg/day. In rabbits,  
387 maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion)  
388 was observed at doses  $\geq 30$  mg/kg/day (approximately 0.007 times the human clinical exposure).  
389 In addition, severe maternal body weight loss and 100% litter loss were observed at doses  
390  $\geq 100$  mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at  
391 doses  $\geq 3$  mg/kg/day (AUC not calculated).

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

### 395 **8.3 Nursing Mothers**

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

### 400 **8.4 Pediatric Use**

401 The safety and effectiveness of VOTRIENT in pediatric patients have not been  
402 established.

403 In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week  
404 administration, toxicities in bone, teeth, and nail beds were observed at doses  $\geq 3$  mg/kg/day  
405 (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day  
406 (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13-  
407 and 26-week studies with rats. Body weight loss and morbidity were observed at these doses.  
408 Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or  
409 absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle,  
410 broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in

411 rats at  $\geq 30$  mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at  
412 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks.

### 413 **8.5 Geriatric Use**

414 In clinical trials with VOTRIENT for the treatment of RCC, 33% (196/582) of patients  
415 were aged  $\geq 65$  years. No overall differences in safety or effectiveness of VOTRIENT were  
416 observed between these patients and younger patients. However, patients  $>60$  years of age may  
417 be at greater risk for an ALT  $>3$  X ULN. In the STS trials, 24% (93/382) of patients were age  
418  $\geq 65$  years. Patients  $\geq 65$  years had increased Grade 3 or 4 fatigue (19% versus 12% for  $<65$ ),  
419 hypertension (10% versus 6%), decreased appetite (11% versus 2%) and ALT (3% versus 2%)  
420 or AST elevations (4% versus 1%). Other reported clinical experience has not identified  
421 differences in responses between elderly and younger patients, but greater sensitivity of some  
422 older individuals cannot be ruled out.

### 423 **8.6 Hepatic Impairment**

424 In clinical studies for VOTRIENT, patients with total bilirubin  $\leq 1.5$  X ULN and AST and  
425 ALT  $\leq 2$  X ULN were included [*see Warnings and Precautions (5.1)*].

426 An analysis of data from a pharmacokinetic study of pazopanib in patients with varying  
427 degrees of hepatic dysfunction suggested that no dose adjustment is required in patients with  
428 mild hepatic impairment [either total bilirubin within normal limit (WNL) with ALT  $>ULN$  or  
429 bilirubin  $>1$  X to  $1.5$  X ULN regardless of the ALT value]. The maximum tolerated dose in  
430 patients with moderate hepatic impairment (total bilirubin  $>1.5$  X to  $3$  X ULN regardless of the  
431 ALT value) was 200 mg per day (N = 11). The median steady-state  $C_{max}$  and  $AUC_{(0-24)}$  achieved  
432 at this dose was approximately 40% and 29%, respectively of that seen in patients with normal  
433 hepatic function at the recommended daily dose of 800 mg. The maximum dose explored in  
434 patients with severe hepatic impairment (total bilirubin  $>3$  X ULN regardless of the ALT value)  
435 was 200 mg per day (N = 14). This dose was not well tolerated. Median exposures achieved at  
436 this dose were approximately 18% and 15% of those seen in patients with normal liver function  
437 at the recommended daily dose of 800 mg. Therefore, VOTRIENT is not recommended in these  
438 patients [*see Clinical Pharmacology (12.3)*].

### 439 **8.7 Renal Impairment**

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

442 There are no clinical or pharmacokinetic data in patients with severe renal impairment or  
443 in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is  
444 unlikely to significantly affect the pharmacokinetics of pazopanib since  $<4\%$  of a radiolabeled  
445 oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 patients  
446 with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of  
447 pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and  
448 dose adjustment is not necessary.

449 **10 OVERDOSAGE**

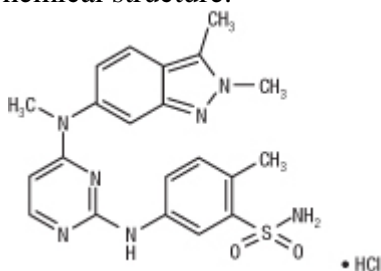
450 Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting  
451 toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed  
452 at 2,000 mg daily and 1,000 mg daily, respectively.

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

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

457 **11 DESCRIPTION**

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



463  
464 Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at  
465 pH 1 and practically insoluble above pH 4 in aqueous media.

466 Tablets of VOTRIENT are for oral administration. Each 200 mg tablet of VOTRIENT  
467 contains 216.7 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base.

468 The inactive ingredients of VOTRIENT are: **Tablet Core:** Magnesium stearate,  
469 microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Gray film-coat:  
470 Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80,  
471 titanium dioxide.

472 **12 CLINICAL PHARMACOLOGY**

473 **12.1 Mechanism of Action**

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

482 **12.2 Pharmacodynamics**

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

485 The QT prolongation potential of pazopanib was assessed in a randomized, blinded,  
486 parallel trial (N = 96) using moxifloxacin as a positive control. Pazopanib 800 mg was dosed  
487 under fasting conditions on Days 2 to 8 and 1,600 mg was dosed on Day 9 after a meal in order  
488 to increase exposure to pazopanib and its metabolites. No large changes (i.e., >20 msec) in QTc  
489 interval following the treatment of pazopanib were detected in this QT trial. The trial was not  
490 able to exclude small changes (<10 msec) in QTc interval, because assay sensitivity below this  
491 threshold (<10 msec) was not established in this trial [see *Warnings and Precautions (5.2)*].

492 **12.3 Pharmacokinetics**

493 Absorption: Pazopanib is absorbed orally with median time to achieve peak  
494 concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean  
495 AUC and C<sub>max</sub> of 1,037 hr•µg/mL and 58.1 µg/mL (equivalent to 132 µM), respectively. There  
496 was no consistent increase in AUC or C<sub>max</sub> at pazopanib doses above 800 mg.

497 Administration of a single pazopanib 400 mg crushed tablet increased AUC<sub>(0-72)</sub> by 46%  
498 and C<sub>max</sub> by approximately 2 fold and decreased t<sub>max</sub> by approximately 2 hours compared to  
499 administration of the whole tablet. These results indicate that the bioavailability and the rate of  
500 pazopanib oral absorption are increased after administration of the crushed tablet relative to  
501 administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets  
502 of VOTRIENT should not be crushed.

503 Systemic exposure to pazopanib is increased when administered with food.  
504 Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2 fold  
505 increase in AUC and C<sub>max</sub>. Therefore, pazopanib should be administered at least 1 hour before or  
506 2 hours after a meal [see *Dosage and Administration (2.1)*].

507 Distribution: Binding of pazopanib to human plasma protein in vivo was greater than  
508 99% with no concentration dependence over the range of 10 to 100 µg/mL. In vitro studies  
509 suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein  
510 (BCRP).

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

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

516 Hepatic Impairment: Mild hepatic impairment was defined as either total bilirubin  
517 WNL with ALT >ULN or bilirubin >1 X to 1.5 X ULN regardless of the ALT value. The median  
518 steady-state pazopanib C<sub>max</sub> and AUC<sub>(0-24)</sub> after a once daily dose of 800 mg/day in patients  
519 (N = 12) with mild impairment were 34 µg/ml (range 11 to 104) and 774 µg•hr/ml (range 215 to  
520 2,034), respectively. These were in a similar range as the median steady-state pazopanib C<sub>max</sub>

521 and  $AUC_{(0-24)}$  in patients (N = 18) with no hepatic impairment (52  $\mu\text{g}/\text{ml}$ , range 17 to 86 and  
522 888  $\mu\text{g}\cdot\text{hr}/\text{ml}$ , range 346 to 1,482, respectively) [*see Dosage and Administration (2.2)*].

523 Moderate hepatic impairment was defined as total bilirubin  $>1.5 \times$  to  $3 \times$  ULN  
524 regardless of the ALT value. The maximum tolerated pazopanib dose in patients with moderate  
525 impairment was 200 mg once daily. The median (N = 11) steady-state  $C_{\text{max}}$  with that regimen  
526 was 22  $\mu\text{g}/\text{ml}$  (range 4.2 to 33), and the median  $AUC_{(0-24)}$  was 257  $\mu\text{g}\cdot\text{hr}/\text{ml}$  (range 66 to 488).  
527 These values were approximately 43% and 29% those of the corresponding median values after  
528 administration of 800 mg once daily in patients with normal hepatic function (N = 18) [*see*  
529 *Dosage and Administration (2.2)*].

530 Severe hepatic impairment was defined as total bilirubin  $>3 \times$  ULN regardless of the  
531 ALT value. Median exposures in patients with severe hepatic impairment receiving 200 mg once  
532 daily (N = 14) were unexpectedly lower than those observed in patients with moderate hepatic  
533 impairment receiving 200 mg once daily. The median steady-state  $C_{\text{max}}$  was 9.4  $\mu\text{g}/\text{ml}$  (range 2.4  
534 to 24), and the median  $AUC_{(0-24)}$  was 131  $\mu\text{g}\cdot\text{hr}/\text{ml}$  (range 47 to 473). These values were  
535 approximately 18% and 15% that of the corresponding median values after administration of  
536 800 mg once daily in patients with normal hepatic function. Despite the observed concentrations,  
537 the dose of 200 mg was not well tolerated in patients with severe hepatic impairment. Use of  
538 VOTRIENT is not recommended in patients with severe hepatic impairment [*see Use in Specific*  
539 *Populations (8.6)*].

540 **Drug Interactions:** Coadministration of multiple doses of oral pazopanib 400 mg with  
541 multiple doses of oral ketoconazole 400 mg (strong CYP3A4/P-gp inhibitor) resulted in a 1.7  
542 fold increase in the  $AUC_{(0-24)}$  and a 1.5 fold increase in the  $C_{\text{max}}$  of pazopanib compared to when  
543 pazopanib was administered alone. Concurrent administration of a single dose of pazopanib eye  
544 drops with ketoconazole in healthy volunteers resulted in a 2 fold and 1.5 fold increase in mean  
545  $AUC_{(0-t)}$  and  $C_{\text{max}}$  values, respectively [*see Dosage and Administration (2.2) and Drug*  
546 *Interactions (7.1)*].

547 Administration of 1,500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp,  
548 and BCRP, with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean  
549 pazopanib  $AUC_{(0-24)}$  and  $C_{\text{max}}$  compared to administration of 800 mg pazopanib alone.

550 In vitro studies with human liver microsomes showed that pazopanib inhibited the  
551 activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction  
552 of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology  
553 studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a  
554 clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate),  
555 warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer  
556 patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and  $C_{\text{max}}$  of  
557 midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of  
558 dextromethorphan to dextrorphan concentrations in the urine after oral administration of  
559 dextromethorphan (CYP2D6 probe substrate). Coadministration of pazopanib 800 mg once daily

560 and paclitaxel 80 mg/m<sup>2</sup> (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean  
561 increase of 26% and 31% in paclitaxel AUC and C<sub>max</sub>, respectively [see *Drug Interactions (7.2)*].

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

## 565 **12.5 Pharmacogenomics**

566 Pazopanib can increase serum total bilirubin levels [see *Warnings and Precautions*  
567 (5.1)]. In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin  
568 for elimination. A pooled pharmacogenetic analysis of 236 Caucasian patients evaluated the TA  
569 repeat polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during  
570 pazopanib treatment. In this analysis, the (TA)<sub>7</sub>/(TA)<sub>7</sub> genotype (UGT1A1\*28/\*28) (underlying  
571 genetic susceptibility to Gilbert's syndrome) was associated with a statistically significant  
572 increase in the incidence of hyperbilirubinemia relative to the (TA)<sub>6</sub>/(TA)<sub>6</sub> and (TA)<sub>6</sub>/(TA)<sub>7</sub>  
573 genotypes.

## 574 **13 NONCLINICAL TOXICOLOGY**

### 575 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

583 Pazopanib may impair fertility in humans. In female rats, reduced fertility including  
584 increased pre-implantation loss and early resorptions were noted at dosages ≥30 mg/kg/day  
585 (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was  
586 seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC).  
587 Post-implantation loss, embryoletality, and decreased fetal body weight were noted in females  
588 administered doses ≥10 mg/kg/day (approximately 0.3 times the human clinical exposure based  
589 on AUC). Decreased corpora lutea and increased cysts were noted in mice given  
590 ≥100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given ≥300 mg/kg/day for  
591 26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC,  
592 respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to  
593 34 weeks (approximately 0.4 times the human clinical exposure based on AUC).

594 Pazopanib did not affect mating or fertility in male rats. However, there were reductions  
595 in sperm production rates and testicular sperm concentrations at doses ≥3 mg/kg/day, epididymal  
596 sperm concentrations at doses ≥30 mg/kg/day, and sperm motility at ≥100 mg/kg/day following  
597 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and  
598 epididymal weights at doses of ≥30 mg/kg/day (approximately 0.35 times the human clinical

599 exposure based on AUC); atrophy and degeneration of the testes with aspermia, hypospermia  
600 and cribiform change in the epididymis was also observed at this dose in the 6-month toxicity  
601 studies in male rats.

## 602 **14 CLINICAL STUDIES**

### 603 **14.1 Renal Cell Carcinoma**

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

611 Of the total of 435 patients enrolled in this trial, 233 patients had no prior systemic  
612 therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or INF $\alpha$ -based  
613 therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics  
614 were balanced between the VOTRIENT and placebo arms. The majority of patients were male  
615 (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were  
616 Asian and less than 1% were other. Forty-two percent were ECOG performance status 0 and  
617 58% were ECOG performance status 1. All patients had clear cell histology (90%) or  
618 predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more  
619 organs involved with metastatic disease. The most common metastatic sites at baseline were lung  
620 (74%), lymph nodes (56%), bone (27%), and liver (25%).

621 A similar proportion of patients in each arm were treatment-naïve and cytokine-  
622 pretreated (see Table 5). In the cytokine-pretreated subgroup, the majority (75%) had received  
623 interferon-based treatment. Similar proportions of patients in each arm had prior nephrectomy  
624 (89% and 88% for VOTRIENT and placebo, respectively).

625 The analysis of the primary endpoint PFS was based on disease assessment by  
626 independent radiological review in the entire trial population. Efficacy results are presented in  
627 Table 5 and Figure 1.

628

629 **Table 5. Efficacy Results in RCC Patients by Independent Assessment**

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

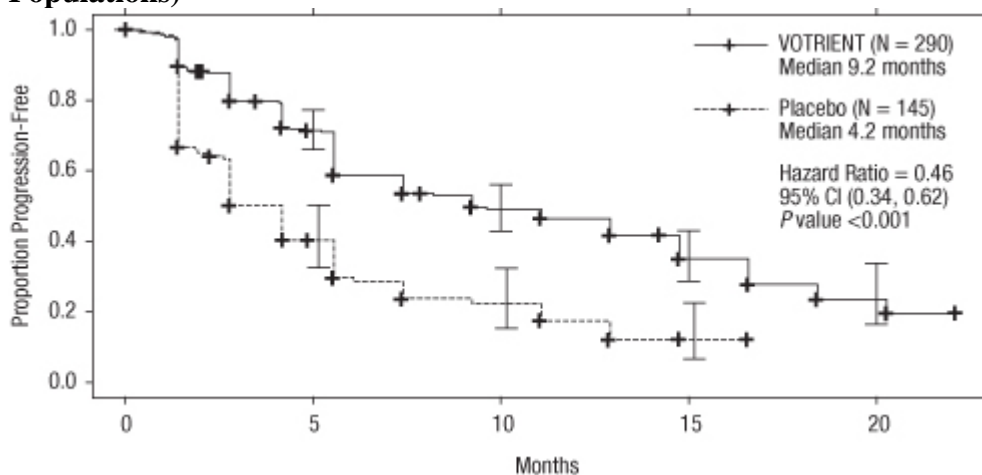
630 HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival; CR = Complete  
631 Response; PR = Partial Response

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

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

634

635 **Figure 1. Kaplan-Meier Curve for Progression-Free Survival in RCC by Independent**  
636 **Assessment for the Overall Population (Treatment-Naïve and Cytokine Pre-Treated**  
637 **Populations)**



638

639

640 At the protocol-specified final analysis of OS, the median OS was 22.9 months for  
641 patients randomized to VOTRIENT and 20.5 months for the placebo arm [HR = 0.91 (95% CI:  
642 0.71, 1.16)]. The median OS for the placebo arm includes 79 patients (54%) who discontinued

643 placebo treatment because of disease progression and crossed over to treatment with  
644 VOTRIENT. In the placebo arm, 95 (66%) patients received at least one systemic anti-cancer  
645 treatment after progression compared to 88 (30%) patients randomized to VOTRIENT.

#### 646 **14.2 Soft Tissue Sarcoma**

647 The safety and efficacy of VOTRIENT in patients with STS were evaluated in a  
648 randomized, double-blind, placebo-controlled, multicenter trial. Patients (N = 369) with  
649 metastatic STS who had received prior chemotherapy, including anthracycline treatment, or were  
650 unsuited for such therapy, were randomized (2:1) to receive VOTRIENT 800 mg once daily or  
651 placebo. Patients with gastrointestinal stromal tumors (GIST) or adipocytic sarcoma were  
652 excluded from the trial. Randomization was stratified by the factors of WHO performance status  
653 (WHO PS) 0 or 1 at baseline and the number of lines of prior systemic therapy for advanced  
654 disease (0 or 1 versus 2+). Progression-free survival (PFS) was assessed by independent  
655 radiological review. Other efficacy endpoints included overall survival (OS), overall response  
656 rate, and duration of response.

657 The majority of patients were female (59%) with a median age of 55 years. Seventy-two  
658 percent of patients were Caucasian, 22% were Asian, and 6% were Other. Forty-three percent of  
659 patients had leiomyosarcoma, 10% had synovial sarcoma, and 47% had other soft tissue  
660 sarcomas. Fifty-six percent of patients had received 2 or more lines of prior systemic therapy and  
661 44% had received 0 or 1 lines of prior systemic therapy. The median duration of treatment was  
662 4.5 months for patients on the pazopanib arm and 1.9 months for patients on the placebo arm.

663 Efficacy results are presented in Table 6 and Figure 2.

664

665 **Table 6. Efficacy Results in STS Patients by Independent Assessment**

| Endpoint/Trial Population            | VOTRIENT                  | Placebo      | HR (95% CI)       |
|--------------------------------------|---------------------------|--------------|-------------------|
| <b>PFS</b>                           |                           |              |                   |
| Overall ITT                          | N = 246                   | N = 123      | 0.35 <sup>a</sup> |
| Median (months)                      | 4.6                       | 1.6          | (0.26, 0.48)      |
| Leiomyosarcoma subgroup              | N = 109                   | N = 49       | 0.37              |
| Median (months)                      | 4.6                       | 1.9          | (0.23, 0.60)      |
| Synovial sarcoma subgroup            | N = 25                    | N = 13       | 0.43              |
| Median (months)                      | 4.1                       | 0.9          | (0.19, 0.98)      |
| 'Other soft tissue sarcoma' subgroup | N = 112                   | N = 61       | 0.39              |
| Median (months)                      | 4.6                       | 1.0          | (0.25, 0.60)      |
| <b>Response Rate (CR + PR)</b>       |                           |              |                   |
| % (95% CI)                           | 4 (2.3, 7.9) <sup>b</sup> | 0 (0.0, 3.0) | —                 |
| Duration of response                 |                           |              |                   |
| Median (months) (95% CI)             | 9.0 (3.9, 9.2)            |              |                   |

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

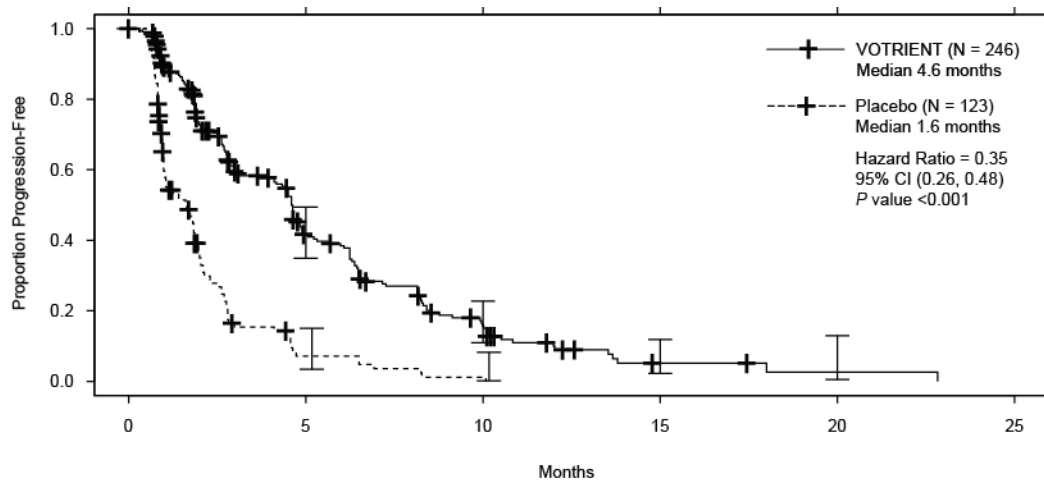
668 <sup>a</sup> P value <0.001

669 <sup>b</sup> There were 11 partial responses and 0 complete responses.

670

671 **Figure 2. Kaplan-Meier Curve for Progression-Free Survival in STS by Independent**  
 672 **Assessment for the Overall Population**

673



674

675

676 At the protocol-specified final analysis of OS, the median OS was 12.6 months for  
 677 patients randomized to VOTRIENT and 10.7 months for the placebo arm [HR = 0.87 (95% CI:  
 678 0.67, 1.12)].

679 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

682 Bottles of 120 tablets: NDC 0173-0804-09

683 Store at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted  
684 to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

685 **17 PATIENT COUNSELING INFORMATION**

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

- 688 • Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor  
689 serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least  
690 once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform  
691 patients that they should report signs and symptoms of liver dysfunction to their healthcare  
692 provider right away.
- 693 • Prolonged QT intervals and torsades de pointes have been observed. Patients should be  
694 advised that ECG monitoring may be performed. Patients should be advised to inform their  
695 physicians of concomitant medications.
- 696 • Cardiac dysfunction (such as CHF and LVEF decrease) has been observed in patients at risk  
697 (e.g., prior anthracycline therapy) particularly in association with development or worsening  
698 of hypertension. Patients should be advised to report hypertension or signs and symptoms of  
699 congestive heart failure.
- 700 • Serious hemorrhagic events have been reported. Patients should be advised to report unusual  
701 bleeding.
- 702 • Arterial thrombotic events have been reported. Patients should be advised to report signs or  
703 symptoms of an arterial thrombosis.
- 704 • Reports of pneumothorax and venous thromboembolic events including pulmonary embolus  
705 have been reported. Patients should be advised to report if new onset of dyspnea, chest pain,  
706 or localized limb edema occurs.
- 707 • Advise patients to inform their doctor if they have worsening of neurological function  
708 consistent with RPLS (headache, seizure, lethargy, confusion, blindness, and other visual and  
709 neurologic disturbances).
- 710 • Hypertension and hypertensive crisis have been reported. Patients should be advised to  
711 monitor blood pressure early in the course of therapy and frequently thereafter and report  
712 increases of blood pressure or symptoms such as blurred vision, confusion, or severe  
713 headache, nausea or vomiting.
- 714 • GI perforation or fistula has occurred. Advise patients to report signs and symptoms of a GI  
715 perforation or fistula.
- 716 • VEGFR inhibitors such as VOTRIENT may impair wound healing. Advise patients to stop  
717 VOTRIENT at least 7 days prior to a scheduled surgery.

- 718 • Hypothyroidism and proteinuria have been reported. Advise patients that thyroid function  
719 testing and urinalysis will be performed during treatment.
- 720 • Serious infections including some with fatal outcomes have been reported. Advise patients to  
721 promptly report any signs or symptoms of infection.
- 722 • Women of childbearing potential should be advised of the potential hazard to the fetus and to  
723 avoid becoming pregnant.
- 724 • Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported  
725 with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their  
726 healthcare provider if moderate to severe diarrhea occurs.
- 727 • Patients should be advised to inform their healthcare providers of all concomitant  
728 medications, vitamins, or dietary and herbal supplements.
- 729 • Patients should be advised that depigmentation of the hair or skin may occur during treatment  
730 with VOTRIENT.
- 731 • Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours  
732 after a meal).
- 733

734 VOTRIENT is a registered trademark of GlaxoSmithKline.  
735



736  
737 GlaxoSmithKline  
738 Research Triangle Park, NC 27709  
739  
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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 get any of these signs of liver problems during treatment with VOTRIENT:**

- 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 area (abdomen)
- bruise easily

Your healthcare provider may need to prescribe a lower dose of VOTRIENT for you or tell you to stop taking VOTRIENT if you develop liver problems during treatment.

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

VOTRIENT is a prescription medicine used to treat people with:

- advanced renal cell cancer (RCC)
- advanced soft tissue sarcoma (STS) who have received chemotherapy in the past.

It is not known if VOTRIENT is effective in treating certain soft tissue sarcomas or certain gastrointestinal tumors.

It is not known if VOTRIENT is safe and 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. You may need a lower dose of VOTRIENT or your

- 41 healthcare provider may prescribe a different medicine to treat your advanced  
42 renal cell cancer or advanced soft tissue sarcoma.
- 43 • have high blood pressure
  - 44 • have heart problems or an irregular heartbeat including QT prolongation
  - 45 • have a history of a stroke
  - 46 • have headaches, seizures, or vision problems
  - 47 • have coughed up blood in the last 6 months
  - 48 • had bleeding of your stomach or intestines in the last 6 months
  - 49 • have a history of a tear (perforation) in your stomach or intestine, or an  
50 abnormal connection between two parts of your gastrointestinal tract (fistula)
  - 51 • have had blood clots in a vein or in the lung
  - 52 • have thyroid problems
  - 53 • had recent surgery (within the last 7 days) or are going to have surgery
  - 54 • have any other medical conditions
  - 55 • are pregnant or plan to become pregnant. VOTRIENT can harm your unborn  
56 baby. You should not become pregnant while you are taking VOTRIENT.
  - 57 • are breastfeeding or plan to breastfeed. It is not known if VOTRIENT passes  
58 into your breast milk. You and your healthcare provider should decide if you will  
59 take VOTRIENT or breastfeed. You should not do both.

60

61 **Tell your healthcare provider about all the medicines you take** including  
62 prescription and non-prescription medicines, vitamins, and herbal supplements.  
63 VOTRIENT may affect the way other medicines work and other medicines may  
64 affect how VOTRIENT works.

65

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

- 67 • take medicines that can affect how your liver enzymes work such as:
  - 68 • certain antibiotics (used to treat infections)
  - 69 • certain medicines used to treat HIV
  - 70 • certain medicines used to treat depression
  - 71 • medicines used to treat irregular heart beats
- 72 • take a medicine that contains simvastatin to treat high cholesterol levels
- 73 • drink grapefruit juice

74

75 Ask your healthcare provider if you are not sure if your medicine is one that is listed  
76 above.

77

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

80

81 **How should I take VOTRIENT?**

- 82 • Take VOTRIENT exactly as your healthcare provider tells you. Your healthcare  
83 provider will tell you how much VOTRIENT to take.  
84 • Your healthcare provider may change your dose.  
85 • Take VOTRIENT on an empty stomach, at least 1 hour before or 2 hours after  
86 food.  
87 • Do not crush VOTRIENT tablets.  
88 • Do not eat grapefruit or drink grapefruit juice during treatment with VOTRIENT.  
89 Grapefruit products may increase the amount of VOTRIENT in your body.  
90 • If you miss a dose, take it as soon as you remember. Do not take it if it is close  
91 (within 12 hours) to your next dose. Just take the next dose at your regular  
92 time. Do not take more than 1 dose of VOTRIENT at a time.  
93 • Your healthcare provider will test your urine, blood, and heart before you start  
94 and while you take VOTRIENT.  
95 • Tell your healthcare provider if you plan to have surgery while taking  
96 VOTRIENT. You will need to stop taking VOTRIENT at least 7 days before  
97 surgery because VOTRIENT may affect healing after surgery.  
98

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

100 **VOTRIENT may cause serious side effects including:**

- 101 • See **“What is the most important information I should know about**  
102 **VOTRIENT?”**
- 103 • **irregular or fast heartbeat or fainting**
- 104 • **heart failure.** This is a condition where your heart does not pump as well as it  
105 should and may cause you to have shortness of breath.
- 106 • **heart attack or stroke.** Heart attack and stroke can happen with VOTRIENT  
107 and may cause death.
- 108 **Symptoms may include:** chest pain or pressure, pain in your arms, back,  
109 neck or jaw, shortness of breath, numbness or weakness on one side of your  
110 body, trouble talking, headache, or dizziness.
- 111 • **blood clots.** Blood clots may form in a vein, especially in your legs (deep vein  
112 thrombosis or DVT). Pieces of a blood clot may travel to your lungs (pulmonary  
113 embolism). This may be life threatening and cause death.
- 114 **Symptoms may include:** new chest pain, trouble breathing or shortness of  
115 breath that starts suddenly, leg pain, and swelling of the arms and hands, or  
116 legs and feet, a cool or pale arm or leg.
- 117 • **bleeding problems.** These bleeding problems may be severe and cause death.  
118 **Symptoms may include:** unusual bleeding, bruising, wounds that do not heal.
- 119 • **tear in your stomach or intestinal wall (perforation) or an abnormal**  
120 **connection between two parts of your gastrointestinal tract (fistula).**

121 **Symptoms may include:** pain, swelling in your stomach-area, vomiting blood,  
122 and black sticky stools.

123 • **Reversible Posterior Leukoencephalopathy (RPLS).** RPLS is a condition  
124 that can happen while taking VOTRIENT that may cause death.

125 **Symptoms may include:** headaches, seizures, lack of energy, confusion, high  
126 blood pressure, blindness or changes in vision, and problems thinking.

127 • **high blood pressure. High blood pressure can happen with VOTRIENT,**  
128 **including a sudden and severe rise in blood pressure which may be life-**  
129 **threatening.** These blood pressure increases usually happen in the first  
130 several months of treatment. Your blood pressure should be well controlled  
131 before you start taking VOTRIENT. Your healthcare provider should begin  
132 checking your blood pressure within 1 week of you starting VOTRIENT and  
133 often during treatment to make sure that your blood pressure is well controlled.

134 **Have someone call your healthcare provider or get medical help right**  
135 **away** for you, if you get symptoms of a severe increase in blood pressure,  
136 including: severe chest pain, severe headache, blurred vision, confusion,  
137 nausea and vomiting, severe anxiety, shortness of breath, seizures, or you pass  
138 out (become unconscious).

139 • **thyroid problems.** Your healthcare provider should check you for this during  
140 treatment with VOTRIENT.

141 • **protein in your urine.** Your healthcare provider will check you for this  
142 problem. If there is too much protein in your urine, your healthcare provider  
143 may tell you to stop taking VOTRIENT.

144 • **serious infections. Serious infections can happen with VOTRIENT and**  
145 **can cause death.**

146 **Symptoms of an infection may include:** fever, cold symptoms, such as  
147 runny nose or sore throat that do not go away, flu symptoms, such as cough,  
148 tiredness, and body aches, pain when urinating, cuts, scrapes or wounds that  
149 are red, warm, swollen or painful.

150 • **collapsed lung (pneumothorax).** A collapsed lung can happen with  
151 VOTRIENT. Air may get trapped in the space between your lung and chest wall.  
152 This may cause you to have shortness of breath.

153

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

156

157 The most common side effects in people who take VOTRIENT include:

- 158 • diarrhea
- 159 • change in hair color
- 160 • nausea or vomiting

161 • loss of appetite

162 Other common side effects in people with advanced soft tissue sarcoma who take  
163 VOTRIENT include:

- 164 • feeling tired
- 165 • decreased weight
- 166 • tumor pain
- 167 • muscle or bone pain
- 168 • headache
- 169 • taste changes
- 170 • trouble breathing
- 171 • change in skin color

172

173 Tell your healthcare provider if you have any side effect that bothers you or that  
174 does not go away.

175

176 These are not all the possible side effects of VOTRIENT. For more information, ask  
177 your healthcare provider or pharmacist.

178

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

181

### 182 **How should I store VOTRIENT tablets?**

183 Store VOTRIENT at room temperature between 68°F and 77°F (20°C to 25°C).

184

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

186

### 187 **General information about the safe and effective use of VOTRIENT.**

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

192

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

198

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

200 **Active ingredient:** pazopanib.

201

202 **Inactive ingredients: Tablet core:** Magnesium stearate, microcrystalline  
203 cellulose, povidone, sodium starch glycolate. **Coating:** Gray film-coat:  
204 Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400),  
205 polysorbate 80, titanium dioxide.

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

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211 GlaxoSmithKline

212 Research Triangle Park, NC 27709

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214 Revised: April 2012

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220 VTR: XMG