

**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.

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 (≥ 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 ≥ 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 ≥ 150 or diastolic blood pressure ≥ 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 ^a	Grade 3	Grade 4	All Grades ^a	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 ^a 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 ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
	%	%	%	%	%	%
Hematologic						
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
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
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 ^a 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 (≥ 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 ≥ 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 ≥ 3 mg/kg/day. In rabbits,
271 maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion)
272 was observed at doses ≥ 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 ≥ 100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at
275 doses ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≤ 1.5 X
307 ULN and AST and ALT ≤ 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 ≥ 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

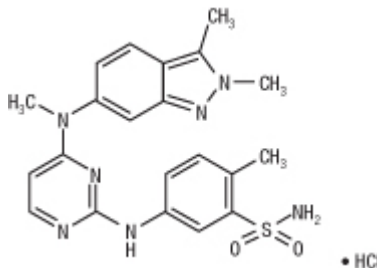
323 Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting
324 toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed
325 at 2,000 mg daily and 1,000 mg daily, respectively.

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)- α
352 and - β , 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- β 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• μ g/mL and 58.1 μ g/mL (equivalent to 132 μ 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₍₀₋₇₂₎ 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 μ 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_(0-t) and C_{max} 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₍₀₋₂₄₎ and C_{max} 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_{max} of
417 midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of
418 dextromethorphan to dextrorphan 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/m² (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean
421 increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively. [See *Drug Interactions*
422 *(7.2).*]

423 In vitro studies also showed that pazopanib inhibits UGT1A1 and OATP1B1 with IC₅₀s
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)⁷/(TA)⁷ 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)⁶/(TA)⁶ and (TA)⁶/(TA)⁷
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 ≥ 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 ≥ 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 ≥ 100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given ≥ 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 ≥ 3 mg/kg/day, epididymal
457 sperm concentrations at doses ≥ 30 mg/kg/day, and sperm motility at ≥ 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 ≥ 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 α -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)
PFS			
Overall ITT Median (months)	N = 290 9.2	N = 145 4.2	0.46 ^a (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)
Response Rate (CR + PR) % (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)	– ^b	

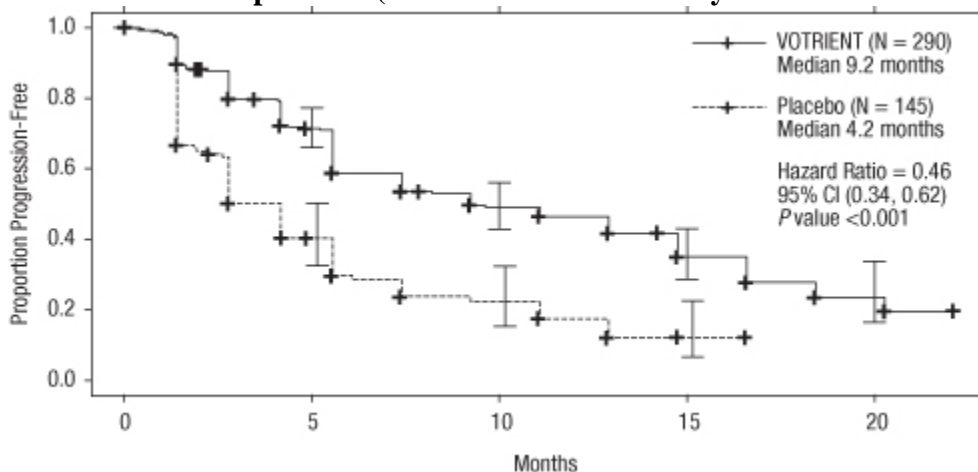
490 HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival; CR = Complete
491 Response; PR = Partial Response

492 ^a P value <0.001

493 ^b 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

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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 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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679 Revised: October 2009

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