

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).]

RECENT MAJOR CHANGES

Warnings and Precautions, Hypertension (5.6) 10/2011

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 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 including hypertensive crisis 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: 10/2011

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: HEPATOTOXICITY**

3 **Severe and fatal hepatotoxicity has been observed in clinical studies. 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™ is indicated for the treatment of patients with advanced renal cell
8 carcinoma (RCC).

9 **2 DOSAGE AND ADMINISTRATION**

10 **2.1 Recommended Dosing**

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

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

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

17 **2.2 Dose Modification Guidelines**

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

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

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

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

36 **3 DOSAGE FORMS AND STRENGTHS**

37 200 mg tablets of VOTRIENT — modified capsule-shaped, gray, film-coated with GS JT
38 debossed on one side. Each tablet contains 216.7 mg of pazopanib hydrochloride equivalent to
39 200 mg of pazopanib.

40 **4 CONTRAINDICATIONS**

41 None.

42 **5 WARNINGS AND PRECAUTIONS**

43 **5.1 Hepatic Effects**

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

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

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

78 **5.2 QT Prolongation and Torsades de Pointes**

79 In clinical RCC studies of VOTRIENT, QT prolongation (≥ 500 msec) was identified on
80 routine electrocardiogram monitoring in 11/558 (<2%) of patients. Torsades de pointes occurred
81 in 2/977 (<1%) of patients who received VOTRIENT in the monotherapy studies.

82 In the randomized clinical trial, 3 of the 290 patients receiving VOTRIENT had post-
83 baseline values between 500 to 549 msec. None of the 145 patients receiving placebo had post-
84 baseline QTc values ≥ 500 msec.

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

90 **5.3 Hemorrhagic Events**

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

96 **5.4 Arterial Thrombotic Events**

97 In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke,
98 and transient ischemic attack [all Grades (3%) and Grades 3 to 5 (2%)] were observed. Fatal
99 events have been observed in 2/586 (0.3%). In the randomized study, these events were observed
100 more frequently with VOTRIENT compared to placebo [see *Adverse Reactions (6.1)*].
101 VOTRIENT should be used with caution in patients who are at increased risk for these events or
102 who have had a history of these events. VOTRIENT has not been studied in patients who have
103 had an event within the previous 6 months and should not be used in those patients.

104 **5.5 Gastrointestinal Perforation and Fistula**

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

108 **5.6 Hypertension**

109 In clinical studies, events of hypertension including hypertensive crisis have occurred.
110 Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should be
111 monitored for hypertension and treated as needed with anti-hypertensive therapy. Hypertension
112 (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) was observed in 47% of
113 patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of

114 treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks).
115 [See *Adverse Reactions (6.1)*.] In the case of persistent hypertension despite anti-hypertensive
116 therapy, the dose of VOTRIENT may be reduced [see *Dosage and Administration (2.2)*].
117 VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension
118 is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT.

119 **5.7 Wound Healing**

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

126 **5.8 Hypothyroidism**

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

130 **5.9 Proteinuria**

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

135 **5.10 Pregnancy**

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

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

145 **6 ADVERSE REACTIONS**

146 **6.1 Clinical Trials Experience**

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

150 Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT
151 prolongation and torsades de pointes, hemorrhagic events, arterial thrombotic events,

152 gastrointestinal perforation and fistula, and hypertensive crisis [see Warnings and Precautions
153 (5.1-5.5)].

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

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

166
167 **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

168 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

169

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

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

179
180 **Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received**
181 **VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus**
182 **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

183 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

184

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

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

197 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension.
198 VOTRIENT has been associated with hypertensive crisis in patients with various cancer types
199 including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive
200 crisis on VOTRIENT. [See Warnings and Precautions (5.6).]

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 (5.2).]

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 (5.3).] 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 (5.8).]

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. [See Warnings and Precautions
234 (5.9).]

235 **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were
236 observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for

237 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC
238 studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%).

239 **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as
240 a decrease in ejection fraction and congestive heart failure) in patients with various cancer types,
241 including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was
242 observed in 4/586 patients (<1%).

243 **7 DRUG INTERACTIONS**

244 **7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

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

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

256 **7.2 Effects of Pazopanib on CYP Substrates**

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

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

264 **8 USE IN SPECIFIC POPULATIONS**

265 **8.1 Pregnancy**

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

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

269 In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic,
270 fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis
271 at a dose level of ≥ 3 mg/kg/day (approximately 0.1 times the human clinical exposure based on
272 AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal
273 subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or
274 absent ossification. In addition, there was reduced fetal body weight, and pre- and post-
275 implantation embryoletality in rats administered pazopanib at doses ≥ 3 mg/kg/day. In rabbits,

276 maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion)
277 was observed at doses ≥ 30 mg/kg/day (approximately 0.007 times the human clinical exposure).
278 In addition, severe maternal body weight loss and 100% litter loss were observed at doses
279 ≥ 100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at
280 doses ≥ 3 mg/kg/day (AUC not calculated).

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

284 **8.3 Nursing Mothers**

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

289 **8.4 Pediatric Use**

290 The safety and effectiveness of VOTRIENT in pediatric patients have not been
291 established.

292 In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week
293 administration, toxicities in bone, teeth, and nail beds were observed at doses ≥ 3 mg/kg/day
294 (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day
295 (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13-
296 and 26-week studies with rats. Body weight loss and morbidity were observed at these doses.
297 Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or
298 absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle,
299 broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in
300 rats at ≥ 30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at
301 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks.

302 **8.5 Geriatric Use**

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

309 **8.6 Hepatic Impairment**

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

313 An interim analysis of data from 12 patients with normal hepatic function and 9 with
314 moderate hepatic impairment showed that the maximum tolerated dose in patients with moderate

315 hepatic impairment was 200 mg per day [see *Clinical Pharmacology (12.3)*]. There are no data
316 on patients with severe hepatic impairment [see *Dosage and Administration (2.2)*].

317 **8.7 Renal Impairment**

318 Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance
319 ≥ 30 mL/min) were included in clinical studies for VOTRIENT.

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

327 **10 OVERDOSAGE**

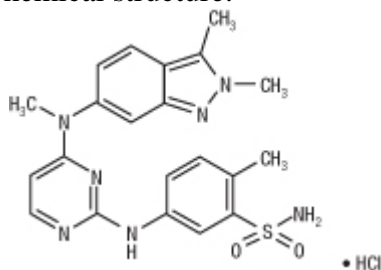
328 Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting
329 toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed
330 at 2,000 mg daily and 1,000 mg daily, respectively.

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

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

335 **11 DESCRIPTION**

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



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

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

345 The inactive ingredients of VOTRIENT are: **Tablet Core:** Magnesium stearate,
346 microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Gray film-coat:
347

348 Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80,
349 titanium dioxide.

350 **12 CLINICAL PHARMACOLOGY**

351 **12.1 Mechanism of Action**

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

360 **12.2 Pharmacodynamics**

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

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

370 **12.3 Pharmacokinetics**

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

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

381 Systemic exposure to pazopanib is increased when administered with food.
382 Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold
383 increase in AUC and C_{max} . Therefore, pazopanib should be administered at least 1 hour before or
384 2 hours after a meal [*see Dosage and Administration (2.1)*].

385 Distribution: Binding of pazopanib to human plasma protein in vivo was greater than
386 99% with no concentration dependence over the range of 10 to 100 μ g/mL. In vitro studies

387 suggest that pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein
388 (BCRP).

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

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

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

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

404 Drug Interactions: Coadministration of oral pazopanib with CYP3A4 inhibitors has
405 resulted in increased plasma pazopanib concentrations. Concurrent administration of a single
406 dose of pazopanib eye drops with the strong CYP3A4 inhibitor and Pgp inhibitor, ketoconazole,
407 in healthy volunteers resulted in 220% and 150% increase in mean AUC_(0-t) and C_{max} values,
408 respectively. [See Dosage and Administration (2.2) and Drug Interactions (7.1).]

409 Administration of 1,500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, Pgp,
410 and BCRP, with 800 mg pazopanib resulted in an approximately 50% to 0% increase in mean
411 pazopanib AUC₍₀₋₂₄₎ and C_{max} compared to administration of 800 mg pazopanib alone.

412 In vitro studies with human liver microsomes showed that pazopanib inhibited the
413 activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction
414 of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology
415 studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a
416 clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate),
417 warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer
418 patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and C_{max} of
419 midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of
420 dextromethorphan to dextrorphan concentrations in the urine after oral administration of
421 dextromethorphan (CYP2D6 probe substrate). Coadministration of pazopanib 800 mg once daily
422 and paclitaxel 80 mg/m² (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean
423 increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively. [See Drug Interactions
424 (7.2).]

425 In vitro studies also showed that pazopanib inhibits UGT1A1 and OATP1B1 with IC50s
426 of 1.2 and 0.79 μ M, respectively. Pazopanib may increase concentrations of drugs eliminated by
427 UGT1A1 and OATP1B1.

428 **12.5 Pharmacogenomics**

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

437 **13 NONCLINICAL TOXICOLOGY**

438 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

446 Pazopanib may impair fertility in humans. In female rats, reduced fertility including
447 increased pre-implantation loss and early resorptions were noted at dosages \geq 30 mg/kg/day
448 (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was
449 seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC).
450 Post-implantation loss, embryoletality, and decreased fetal body weight were noted in females
451 administered doses \geq 10 mg/kg/day (approximately 0.3 times the human clinical exposure based
452 on AUC). Decreased corpora lutea and increased cysts were noted in mice given
453 \geq 100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given \geq 300 mg/kg/day for
454 26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC,
455 respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to
456 34 weeks (approximately 0.4 times the human clinical exposure based on AUC).

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

463 and cribiform change in the epididymis was also observed at this dose in the 6-month toxicity
464 studies in male rats.

465 **14 CLINICAL STUDIES**

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

473 Of the total of 435 patients enrolled in this study, 233 patients had no prior systemic
474 therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or INF α -based
475 therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics
476 were balanced between the VOTRIENT and placebo arms. The majority of patients were male
477 (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were
478 Asian and less than 1% were other. Forty-two percent were ECOG performance status 0 and
479 58% were ECOG performance status 1. All patients had clear cell histology (90%) or
480 predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more
481 organs involved with metastatic disease. The most common metastatic sites at baseline were lung
482 (74%), lymph nodes (56%), bone (27%), and liver (25%).

483 A similar proportion of patients in each arm were treatment-naïve and cytokine-
484 pretreated (see Table 3). In the cytokine-pretreated subgroup, the majority (75%) had received
485 interferon-based treatment. Similar proportions of patients in each arm had prior nephrectomy
486 (89% and 88% for VOTRIENT and placebo, respectively).

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

490

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

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

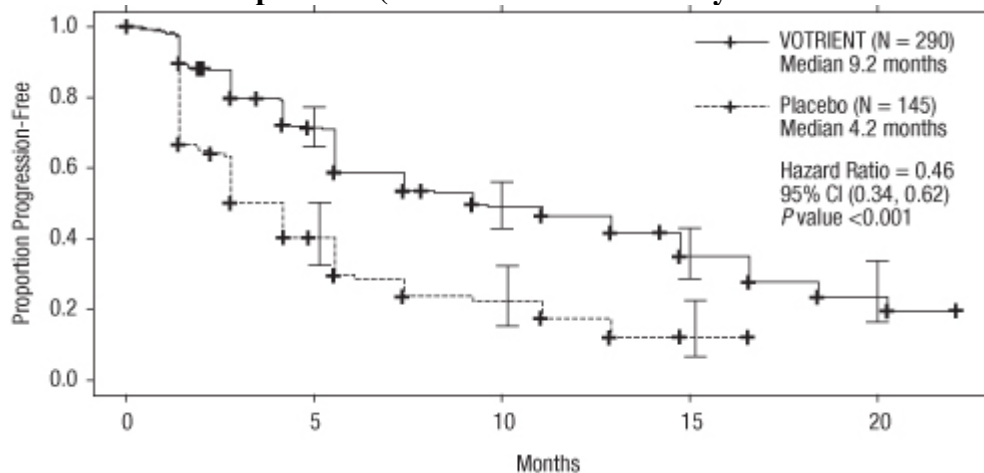
492 HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival; CR = Complete
493 Response; PR = Partial Response

494 ^a P value <0.001

495 ^b There were only 5 objective responses.

496

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



499

500

501 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

504 Bottles of 120 tablets: NDC 0173-0804-09
505 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP
506 Controlled Room Temperature].

507 **17 PATIENT COUNSELING INFORMATION**

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

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

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532



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535 Research Triangle Park, NC 27709
536
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538 Month YEAR
539 VTR:XPI