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

Dosage and Administration, Dose Modification Guidelines. (2.2)	03/2012
Warnings and Precautions, Hepatic Effects. (5.1)	03/2012
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)
- 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 (≥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)
- Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY
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).]*

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

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

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

2.2 Dose Modification Guidelines

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

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

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

Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided.

VOTRIENT should not be used in patients who can not avoid chronic use of strong CYP3A4 inducers. *[See Drug Interactions (7.1).]*

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Effects

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

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

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

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

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

5.2 QT Prolongation and Torsades de Pointes

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

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

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

5.3 Hemorrhagic Events

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

5.4 Arterial Thrombotic Events

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

5.5 Gastrointestinal Perforation and Fistula

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

5.6 Hypertension

In clinical studies, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy. Hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). *[See Adverse Reactions (6.1).]* In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced *[see Dosage and Administration (2.2)]*. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT.

5.7 Wound Healing

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

5.8 Hypothyroidism

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

5.9 Proteinuria

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

5.10 Pregnancy

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

There are no adequate and well-controlled studies of VOTRIENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential

should be advised to avoid becoming pregnant while taking VOTRIENT. *[See Use in Specific Populations (8.1).]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

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

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

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

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

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

Hypertension: In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. *[See Warnings and Precautions (5.6).]*

QT Prolongation and Torsades de Pointes: In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.2).]*

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

Hemorrhagic Events: In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.3).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT.

Hypothyroidism: In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.8).]*

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

Proteinuria: In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. *[See Warnings and Precautions (5.9).]*

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

Cardiac Dysfunction: Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types,

including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

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

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

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

7.2 Effects of Pazopanib on CYP Substrates

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

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

7.3 Effect of Concomitant use of VOTRIENT and Simvastatin

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis

at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered pazopanib at doses ≥3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated).

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

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

8.7 Renal Impairment

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

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

10 OVERDOSAGE

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

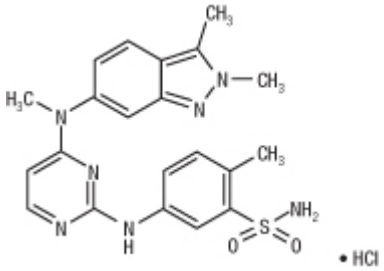
Treatment of overdose with VOTRIENT should consist of general supportive measures. There is no specific antidote for overdosage of VOTRIENT.

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

11 DESCRIPTION

VOTRIENT (pazopanib) is a tyrosine kinase inhibitor (TKI). Pazopanib is presented as the hydrochloride salt, with the chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride. It has

the molecular formula $C_{21}H_{23}N_7O_2S$•HCl and a molecular weight of 473.99. Pazopanib hydrochloride has the following chemical structure:



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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

The QT prolongation potential of pazopanib was assessed in a randomized, blinded, parallel study (N = 96) using moxifloxacin as a positive control. Pazopanib 800 mg was dosed under fasting conditions on Days 2 to 8 and 1,600 mg was dosed on Day 9 after a mea1 in order to increase exposure to pazopanib and its metabolites. No large changes (i.e., >20 msec) in QTc interval following the treatment of pazopanib were detected in this QT study. The study was not able to exclude small changes (<10 msec) in QTc interval, because assay sensitivity below this threshold (<10 msec) was not established in this study. *[See Warnings and Precautions (5.2).]*

12.3 Pharmacokinetics

<u>Absorption:</u> Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean

AUC and C_{max} of 1,037 hr•μg/mL and 58.1 μg/mL (equivalent to 132 μM), respectively. There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

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

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

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

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

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

Hepatic Impairment: Mild hepatic impairment was defined as either total bilirubin WNL with ALT > ULN or bilirubin > 1 X to 1.5 X ULN regardless of the ALT value. The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ after a once daily dose of 800 mg/day in patients (N = 12) with mild impairment were 34 μg/ml (range 11 to 104) and 774 μg•hr/ml (range 215 to 2,034), respectively. These were in a similar range as the median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients (N = 18) with no hepatic impairment (52 μg/ml, range 17 to 86 and 888 μg•hr/ml, range 346 to 1,482, respectively) *[see Dosage and Administration (2.2)]*.

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

Severe hepatic impairment was defined as total bilirubin > 3 X ULN regardless of the ALT value. Median exposures in patients with severe hepatic impairment receiving 200 mg once daily (N=14) were unexpectedly lower than those observed in patients with moderate hepatic impairment receiving 200 mg once daily. The median steady-state C_{max} was 9.4 μg/ml (range 2.4

to 24), and the median $AUC_{(0-24)}$ was 131 µg•hr/ml (range 47 to 473). These values were approximately 18% and 15% that of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function. Despite the observed concentrations, the dose of 200 mg was not well tolerated in patients with severe hepatic impairment. Use of VOTRIENT is not recommended in patients with severe hepatic impairment. *[See Use in Specific Populations (8.6).]*

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

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

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

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

12.5 Pharmacogenomics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

14 CLINICAL STUDIES

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

Of the total of 435 patients enrolled in this study, 233 patients had no prior systemic therapy (treatment-naïve subgroup) and 202 patients received one prior IL-2 or INFα-based therapy (cytokine-pretreated subgroup). The baseline demographic and disease characteristics

were balanced between the VOTRIENT and placebo arms. The majority of patients were male (71%) with a median age of 59 years. Eighty-six percent of patients were Caucasian, 14% were Asian and less than 1% were other. Forty-two percent were ECOG performance status 0 and 58% were ECOG performance status 1. All patients had clear cell histology (90%) or predominantly clear cell histology (10%). Approximately 50% of all patients had 3 or more organs involved with metastatic disease. The most common metastatic sites at baseline were lung (74%), lymph nodes (56%), bone (27%), and liver (25%).

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

The analysis of the primary endpoint PFS was based on disease assessment by independent radiological review in the entire study population.

Efficacy results are presented in Table 3 and Figure 1.

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]	

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

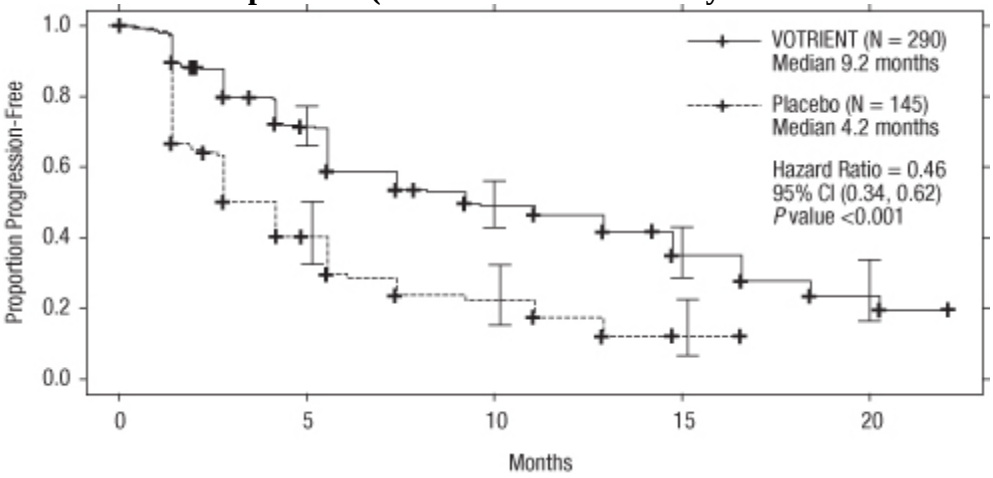
[a] *P* value <0.001

[b] There were only 5 objective responses.

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

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

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



16 HOW SUPPLIED/STORAGE AND HANDLING

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

Bottles of 120 tablets: NDC 0173-0804-09

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

17 PATIENT COUNSELING INFORMATION

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

- Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away.
  - yellowing of the skin or the whites of the eyes (jaundice),
  - unusual darkening of the urine,
  - unusual tiredness,
  - right upper stomach area pain.

- Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- Patients should be advised that depigmentation of the hair or skin may occur during treatment with VOTRIENT.
- Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours after a meal).

VOTRIENT is a registered trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

March 2012
VTR:XPI