CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 19, 2009
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-465
Applicant Name	GlaxoSmithKline
Date of Submission	December 19, 2008
PDUFA Goal Date	October 19, 2008
Proprietary Name / **Established (USAN) Name**	VOTRIENT/ pazopanib
Dosage Forms / Strength	Tablets/200 mg and 400 mg
Proposed Indication(s)	VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Yang-Min (Max) Ning
Statistical Review	Yu-Ling Chang, Shenghui Tang
Pharmacology Toxicology Review	Robeena Aziz, Whitney Helms, Leigh Verbois
CMC Review/OBP Review	Sharmista Chatterjee, Bogdan Kurtyka, Brian Rogers
Microbiology Review	N/A
Clinical Pharmacology Review	Bahru Habtemariam
DDMAC	Keith Olin, Stephanie Victor
DSI	Robert Young
CDTL Review	Ellen Maher
OSE/DMEPA	Lori Cantin
OSE/DDRE	N/A
OSE/DRISK	Shawna Hutchins
QT-IRT	Suchitra Balakrishnan

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application seeks approval of VOTRIENT (pazopanib) tablets for the indication of treatment of patients with advanced renal cell cancer. The application was received on 12/19/09 and the PDUFA date is 10/19/09. This review will summarize the efficacy and safety data which support approval and will provide the recommendations of each review discipline.

2. Background

As noted in the agreed upon package insert, "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). "

This application is primarily supported by safety and efficacy data from a randomized, placebo-controlled trial. In September 2005 the applicant submitted a SPA which proposed a trial in patients with advanced renal cell cancer with disease progression following cytokine-based therapy. In March 2006 the applicant proposed a protocol amendment to also include treatment naïve patients. Given the availability of two other drugs (sorafenib and sunitinib) that had been recently approved in the U.S. for the treatment of advanced renal cell cancer, the FDA expressed concerns about the use of a placebo control and agreement was not reached on the study design. The study was conducted outside of the U.S. where sorafenib and sunitinib were not available.

3. CMC/Device

The CMC Review of 10/7/09 stated that "NDA# 22-465 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending the receipt of an overall acceptable recommendation from the Office of Compliance."

The ONDQA Division Director's Memo of 10/8/09 stated that "This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending the receipt of an overall acceptable recommendation from the Office of Compliance." Based on discussions with the clinical and clinical pharmacology review teams regarding the possible need for a smaller dosage form to allow for dose reduction in patients with hepatotoxicity, the following PMC language was proposed:

Develop a 100 mg dosage form (tablet) to allow for proper dose reductions when Votrient™ (Pazopanib) liver enzyme elevations occur. The 100 mg tablet strength should be sufficiently distinguishable from the 200 mg and 400 mg tablets. (b) (4)

The Final CMC recommendation dated 10/15/09 stated the following:

This memo serves to update the determination of approvability for NDA 22-465 from a Chemistry, Manufacturing and Controls standpoint. The Office of Compliance issued an overall acceptable recommendation for this application on 09-OCT-2009. Accordingly, approval of NDA 22-465 is now recommended.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. I concur with the proposed PMC. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation dated 9/18/09 stated that the application was approvable and that the non-clinical studies with pazopanib support the safety of its use in renal cell carcinoma. No additional non-clinical studies were recommended. The Supervisory Pharmacologist Memorandum and Associate Director for Pharmacology memo concurred.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 9/21/09 provided the following summary:

To support the efficacy in advanced RCC, the sponsor conducted one randomized, controlled phase 3 study. Subjects in the phase 3 study were randomized to receive placebo or pazopanib at 800 mg once daily (qd). Median progression free survival (PFS), the primary endpoint, of the placebo and pazopanib treated patients was 4.2 and 9.2 months, respectively. Compared to placebo, pazopanib was efficacious in extending PFS in RCC patients. No exposure-response relationship was present between PFS and pazopanib trough concentrations. However, a clear exposure-response relationship was detected between ALT (alanine aminotransferase) and pazopanib trough concentrations.

Pazopanib has a bioavailability range of 14-39%, and absorption peaks at 2-8 hours post dose. Pazopanib is mainly metabolized by CYP3A4 and to a lesser extent by CYP1A2 and CYP2C8. In plasma, pazopanib metabolites accounted for less <10% of administered drug.

In a drug-drug interaction study using ocular pazopanib and oral ketocoanzole, pazopanib Cmax and AUC were increased 1.5- and 2.2-fold. When coadministered with lapatinib, a weak CYP3A4 inhibitor, pazopanib Cmax and AUC increased by 60% and 50 %. Enzyme inducing anti-convulsants decreased pazopanib AUC and Cmin by 30% and 50 %, respectively.

A food effect study was also performed using low and high fat meals. Low fat meals increased Cmax and AUC by 1.9 and 2.1-fold, whereas high fat meals increased Cmax and AUC by 2.1 and 2.3-fold. To minimize unintended over exposure, the sponsor proposes to administer pazopanib without food.

Finally, a pooled (phase I-III) pharmacogenetic analysis of alanine aminotransferase (ALT) and total bilirubin (TBL) elevations in pazopanib-treated patients was performed. Variation in the hemachromatosis gene (HFE) and UGT1A1 were associated with elevations in ALT and TBL, respectively. The UGT1A1-TBL association is supported by the inhibition of UGT1A1 in vitro by pazopanib.

The review made the following recommendations:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-465. This NDA is considered acceptable from a clinical pharmacology perspective.

Post Marketing Requirements

1. The applicant should conduct a drug-drug interaction study using oral pazopanib and a strong CYP3A4 inhibitor (e.g. ketocoanzole)
2. Submit the complete study report of the on going hepatic impairment study (Study NCI 8063)
3. Submit the complete study report of the QT/QTc evaluation study (study VEG111485).

Post Marketing Commitment

1. In order to support appropriate dose modifications, you should develop a 100 mg formulation.

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval and with the recommended PMR's and PMC.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The randomized study design and efficacy results are provided in the following excerpt from the Clinical Studies section of the agreed-upon package insert.

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. OS data were not mature at the time of the interim survival analysis. Efficacy results are presented in Table 3 and Figure 1.

Table 3. Efficacy Results by Independent Assessment

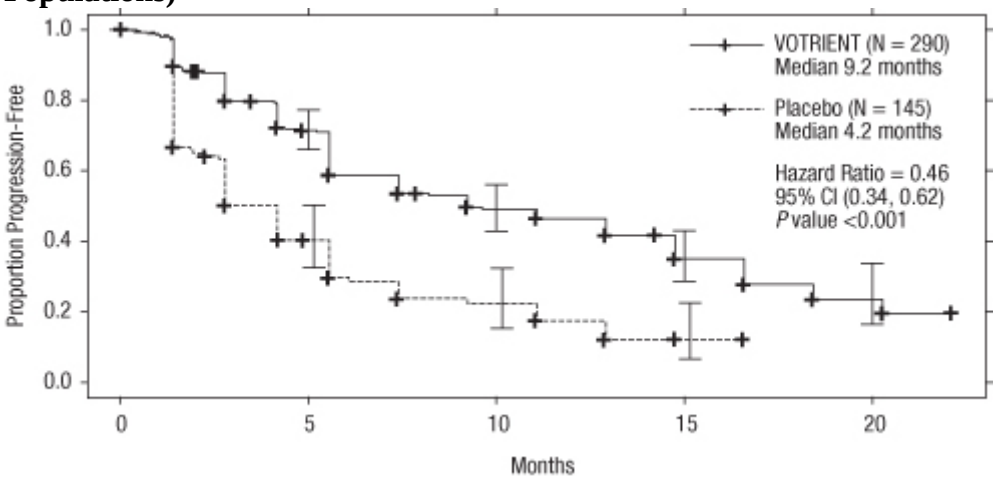
Endpoint/Study Population	VOTRIENT	Placebo	HR (95% CI)
PFS			
Overall ITT	N = 290	N = 145	
Median (months)	9.2	4.2	0.46[a] (0.34, 0.62)
Treatment-naïve subgroup	N = 155 (53%)	N = 78 (54%)	
Median (months)	11.1	2.8	0.40 (0.27, 0.60)
Cytokine pre-treated subgroup	N = 135 (47%)	N = 67 (46%)	
Median (months)	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.

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



The Clinical Review of 10/14/09 made the following recommendation on regulatory action.

The reviewers examined the submitted data and study reports and found that the application provided adequate efficacy and safety evidence to support the use of pazopanib in patients with advanced RCC. The reviewers concur with the applicant's conclusions about pazopanib in support of the proposed indication.

The reviewers recommend regular approval of pazopanib at the proposed dosing schedule for the treatment of patients with advanced RCC. This is based on the findings of a robust improvement in progression-free survival (PFS) with pazopanib in a placebo-controlled study and of an acceptable safety profile for pazopanib as demonstrated in the submitted clinical studies of the product.

The review recommended the following PMC's and PMR's

- To complete and submit the final study report and datasets for the ongoing trial entitled "VEG108844: A Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma". The specified dates for this requirement are as follows.

  Original Protocol Submission: 05/2008
  Expected Trial Completion Date: 12/2010
  Final Study Report and Dataset Submission: 05/2011

- Conduct a study of at least 1500 patients to assess the safety of the current dose modification plan for pazopanib and the safety of re-challenge with pazopanib following hepatotoxicity. Patients from ongoing studies with pazopanib may be included in this study. Dates for submission of a protocol, trial completion, submission of the clinical study report, associated datasets, and any changes in product labeling, if needed, are pending.

- Submit the final analysis of OS from "VEG105192: A Randomized, Double-Blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

The Statistical Review and Evaluation of 9/15/09 provided the following conclusions and recommendations:

On 19 December 2008, the sponsor submitted an application to evaluate the efficacy and safety of single-agent GW786034 (Pazopanib, Votrient®), a new molecular entity (NME), in patients with locally advanced and/or metastatic renal cell carcinoma. In this application, the sponsor submitted the efficacy and safety data from Study VEG105192, "A Randomized, Double-blind, Placebo-controlled, Multi-center Phase III Study to Evaluate the Efficacy and Safety of Pazopanib (GW786034) Compared to Placebo in Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

The primary efficacy endpoint in Study VEG 10592 was progression free survival (PFS). The primary PFS efficacy analysis of Study VEG105192 in the ITT population was based on PFS data assessed by the independent review committee (IRC). At the time of data cutoff for the final PFS analysis (23 May 2008), 435 subjects were randomized in a 2:1 ratio: 290 in the pazopanib arm and 145 in the placebo arm. The PFS analysis included 148 events (51%) for PFS in the

pazopanib arm and 98 events (68%) for PFS in the placebo arm. The estimated medians of PFS in the pazopanib arm and the placebo arm were 9.2 months and 4.2 months respectively. The adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.46 (p-value < 0.0000001). The un-adjusted hazard ratio for recurrence or death in the pazopanib arm, as compared with the placebo arm, was 0.44 (p-value < 0.0001).

At the time of PFS analysis, a planed interim analysis for overall survival (OS) included 109 (38%) in pazopanib arm and 67 (46%) deaths in placebo arm. The estimated medians of OS in the pazopanib arm and the placebo arm were 21.1 months and 18.7 months respectively. The adjusted hazard ratio for death in the pazopanib arm, as compared with the placebo arm, was 0.73 (p-value = 0.02), which was not statistically significant. The final OS survival analysis will be conducted when 287 deaths occur. However, given the 48% (70 subjects) rate of crossover from placebo to pazopanib in the extension study, longer follow up is unlikely to demonstrate a statistically significant difference in overall survival.

This application will be discussed at the Oncology Drugs Advisory Committee meeting on October 5, 2009.

The Statistical Team Leader Memo of 9/16/09 concurred with the statistical reviewer.

The CDTL Review of 10/13/09 provided the following recommendation and risk:benefit assessment:

- Recommended Regulatory Action: Regular Approval
- Risk Benefit Assessment: Pazopanib has shown a clear benefit in patients with renal cell carcinoma. The magnitude of the risk with pazopanib is consistent with that of other products approved for this indication.
    - Risk
        - The risks of pazopanib are consistent with those of other products that act through the vascular endothelial growth factor pathway.
        - Additional risks that cannot be clearly attributed to this pathway include hepatotoxicity, torsades de pointes, and hand-foot syndrome.
        - The risk of hepatic failure appears to be low and may be manageable with dose adjustment.
    - Benefit
        - Pazopanib has shown a statistically significant, 5 month improvement in progression-free survival in patients with metastatic or locally advanced renal cell carcinoma.
        - Pazopanib has shown a numerically, but not statistically significant improvement in overall survival.

The review recommended the following PMR's and PMC:

The following post-marketing requirements will be included in the letter to the applicant.

1. Submit the final analysis of overall survival from the Phase 3 trial comparing pazopanib to placebo (VEG105192).
2. Submit a report, from several ongoing trials, concerning the safety of pazopanib dose modification and rechallenge in patients with elevated ALT.
3. Submit a final report concerning the cardiotoxicity of pazopanib, including the effect of pazopanib on ejection fraction, from the ongoing trial, VEG108844.
4. Submit the final report of the ongoing hepatic impairment trial, NCI 8063.
5. Conduct a clinical trial of the effect of pazopanib on QTc prolongation and submit a final report.
6. Conduct a clinical trial studying the influence of strong CYP3A4 inhibitors on serum pazopanib levels and submit a final study report.

The following post-marketing commitment will also be included in the letter to the applicant.

7. Develop a 100 mg dosage form of pazopanib to allow for proper dose reductions in patients with an elevated ALT.

8. Safety

The safety profile of pazopanib is summarized in the following excerpt from the agreed-upon package insert:

The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies which included 586 patients with RCC. 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.

Additional toxicities of concern in the Adverse Reactions section which are also addressed in the Warnings and Precautions section are provided below:

> 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…
>
> 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. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT…

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…

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)…

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... 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…

Additional significant laboratory abnormalites addressed in the Adverse Reactions section include proteinuria, lipase elevations, and pancreatitis.

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.

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%).

9. Advisory Committee Meeting

The application was discussed at a meeting of the Oncologic Drugs Advisory Committee on October 5, 2009. ODAC was asked to vote on the following question: "Is the benefit-to-risk profile demonstrated for pazopanib acceptable for the treatment of patients with advanced RCC?" The committee voted 10 to 0 that benefit to risk profile was acceptable.

10. Pediatrics

PeRC granted a waiver for pediatric studies required by PREA.

11. Other Relevant Regulatory Issues

- DSI Audits

  The Clinical Inspection Summary concluded the following:

  Three foreign clinical investigator inspections were conducted in support of the NDA. For two sites (Drs. Rolski and Koralewski), no regulatory violations were noted. For the third site (Dr. Lee), although regulatory violations were noted, it is unlikely that they will impact data integrity. The data from all three sites are acceptable in support of the pending application.

- Financial Disclosure

  Financial disclosure was discussed on page 19 of the Clinical Review. No issues were identified.

- The DDMAC consult recommendations of 10/13/09 were discussed in the labeling meetings.

- The SEALD labeling recommendations of 10/2/09 were discussed in the labeling meeting.

- The QT-IRT review concluded the following:

1. To date there have been two cases of Torsade de Pointes in the clinical program along with two cases of sudden death in younger patients with no pre-existing cardiac disease. The QT effect has not been well characterized. The relationship between ΔQTcF (change from baseline) and pazopanib concentrations from study VEG10003 is visualized in Figure 1 (bottom) with no evident exposure-response relationship. However, ECGs were not collected at steady state C_{max}: the drug accumulates and post-dose ECGs were only collected on day 1 (see highlights of clinical pharmacology in Table 1). Furthermore,

   only single ECGs were collected at each time-point and they were not centrally read, thereby increasing variability. Hence the reliability of the concentration-QTc analysis showing no exposure-response relationship is questionable.
2. The sponsor plans to conduct a dedicated QT study in patients (VEG111485) and the IRT has reviewed the protocol (see IRT Review dated June 20, 2008 for IND 65747). This study will not be completed until after the action date for this NDA.

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name

  DMEPA concluded that the proprietary name VOTRIENT was acceptable.

- Physician labeling

  Agreement was reached with the applicant on the physician labeling.

- Carton and immediate container labels

  The revised carton and container labels are acceptable.

- Medication Guide

  The applicant agreed to the changes in the Medication Guide recommended by DRISK.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

The median PFS in the overall population by independent review was 9.2 months in the pazopanib group compared to 4.2 months in the placebo group (HR=0.46, p<0.001). The effect size was larger in the treatment-naïve subgroup (11.1 vs. 2.8 months, HR=0.40) but was also clinically significant in the cytokine-pretreated group (7.4 vs. 4.2 months, HR=0.54). The objective response rate in the pazopanib group was 30% with a median duration of response of 58.7 weeks. Although the survival data are not mature, there is a trend in favor of the pazopanib group. These results are comparable to those of other agents recently approved for the treatment of advanced renal cell carcinoma.

The most commonly observed adverse reactions (≥20%) were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. Other toxicities of concern include hepatotoxicity, hypertension, QT prolongation and torsades de pointes, arterial thrombotic events, hemorrhagic events, hypothyroidism, diarrhea, gastrointestinal perforation/fistula, proteinuria, and lipase elevations.

The safety profile and risk benefit ratio was discussed in detail at the October 5, 2009 meeting of the Oncologic Drugs Advisory Committee meeting. The committee voted unanimously that the risk benefit profile was acceptable for this indication.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  The applicant agreed to a REMS that consists of a Medication Guide to inform patients of the risks and benefits of pazopanib and the need for laboratory monitoring.

- Recommendation for other Postmarketing Requirements and Commitments

The following are postmarketing requirements:

1. Examine the safety of dose modification of pazopanib and patient rechallenge with pazopanib following hepatotoxicity. This examination should include at least 1,500 treated patients and may be derived from ongoing or completed trials(s) including VEG108844, VEG110727, and VEG110665.

   Trial Completion Date: 7/31/2012
   Final Report Submission: 10/31/2012

2. Examine the cardiotoxicity, clinical cardiac events and changes in ejection fraction, in your ongoing trial VEG108844.

   Final Protocol Submission: 05/29/2008
   Trial Completion Date: 12/31/2010
   Final Report Submission: 05/31/2011

3. Submit the final report of the hepatic impairment trial, protocol NCI 8063.

   Final Protocol Submission: 10/19/2007
   Trial Completion Date: 1/15/2010
   Final Report Submission: 5/15/2010

4. Submit the report of the dedicated QTc prolongation trial, VEG111485.

   Final Protocol Submission: 1/27/2009
   Trial Completion Date: 2/27/2010
   Final Report Submission: 7/30/2010

5. To adequately determine the influence of strong CYP3A4 inhibitors on the exposure of pazopanib following oral clinical pazopanib doses, conduct a drug-drug interaction trial in patients using clinical doses of oral pazopanib and a strong CYP3A4 inhibitor (e.g. ketocoanzole). The protocol should be submitted prior to initiation for review and concurrence.

   Final Protocol Submission: 1/15/2010
   Trial Completion Date: 10/31/2010
   Final Report Submission: 2/28/2011

The following are postmarketing study commitments:

6. Submit the final analysis of overall survival in your ongoing trial VEG105192.

   Final Protocol Submission: 2/03/2006
   Trial Completion Date: 1/31/2010
   Final Report Submission: 5/31/2010

7. Pending the outcome of trials VEG 108844, 110727, or NCI 8063, you may need to develop a 100 mg dosage form (tablet) to allow for proper dose reductions of Votrient™ (Pazopanib) when liver enzyme elevations occur. The 100 mg dosage form should be sufficiently distinguishable from the 200 mg and 400 mg tablets. (b) (4)

   Final Protocol Submission: 9/30/2010
   Final Report Submission: 12/31/2011

8. Submit the final report with complete datasets for ongoing trial VEG108844 titled: A Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

   Final Protocol Submission: 5/29/2008
   Trial Completion Date: 12/31/2010
   Final Report Submission: 5/31/2011

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/s/

ROBERT L JUSTICE
10/19/2009