CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

OFFICE DIRECTOR MEMO

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Date	October 19, 2009
From	Richard Pazdur, MD
Subject	Office Director Memo
NDA/BLA # Supplement#	22-465
Applicant	GlaxoSmithKline
Date of Submission	December 12, 2008
PDUFA Goal Date	October 19, 2009
Proprietary Name / Established (USAN) names	Votrient/Pazopanib
Dosage forms / Strength	Tablet/200 mg and 400 mg
Proposed Indication(s)	Treatment of patients with advanced renal cell cancer
Recommended:	Regular Approval

Summary:

On October 19, 2009, the U. S. Food and Drug Administration granted approval to pazopanib tablets (VOTRIENT®, GlaxoSmithKline) for the treatment of patients with advanced renal cell carcinoma.

The efficacy and safety of pazopanib were evaluated in an international, multicenter, randomized, double-blind trial comparing pazopanib to placebo. All patients received best supportive care. The trial was conducted in patients with metastatic renal cell carcinoma who were treatment naïve or who had received prior cytokine therapy. Randomization was stratified according to performance status, prior nephrectomy, and prior cytokine therapy.

A total of 435 patients were randomized (2:1) to receive pazopanib (n=290) or placebo (n=145). Demographics were balanced between the two arms. Progression-free survival (PFS) was the trial's primary endpoint. The median PFS was 9.2 and 4.2 months in the pazopanib and placebo arms, respectively (HR = 0.46, p value < 0.001). The treatment effect was similar in the treatment naïve and cytokine pre-treated populations. The overall survival results are not mature; 40% of patients had died by the time of data cut-off. The objective response rates were 30% and 3% for pazopanib and placebo, respectively. After documented radiological progression, patients receiving placebo could receive pazopanib.

The most common adverse reactions (≥20%) were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. Grade 3/4 adverse reactions that differed by ≥2% between arms were abnormal hepatic function, diarrhea, hypertension, and proteinuria. QT prolongation has been seen and the EKG and electrolytes should be monitored. Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the pazopanib arm included increased transaminases, hyperglycemia, leukopenia, hyperbilirubinemia, neutropenia, hypophosphatemia, thrombocytopenia, lymphocytopenia, hyponatremia, hypomagnesemia, and hypoglycemia. Deaths (≤1% of the patients) due to CVA, gastric cancer, GI hemorrhage, hemoptysis, bowel perforation, cardiac failure, MI, and pneumonia occurred more commonly on the pazopanib arm.

Hepatic dysfunction is included as a boxed warning in the product label. Liver tests should be monitored every 4 weeks for at least the first 4 months with periodic monitoring thereafter. Recommended dose modifications for pazopanib in patients with abnormal liver tests are included in the package insert.

The recommended dose of pazopanib for treatment of advanced renal cell carcinoma is 800 mg, once daily at the same time without food (at least 1 hour before or 2 hours after a meal).

GlaxoSmithKline submitted a New Drug Application for pazopanib for the indication of the treatment of patients with advanced renal cell cancer. Pazopanib is a multi-kinase inhibitor. This included inhibition of the vascular endothelial growth factor receptor (VEGFR). The key study in this application was a single Phase 3 trial which examined progression-free survival (PFS) in treatment-naïve and cytokine pre-treated patients with metastatic or locally advanced renal cell carcinoma. This was supported by safety and efficacy data from two Phase 2 studies in renal cell cancer as well as safety data from their pazopanib monotherapy program (in a variety of tumor types

The applicant was advised to conduct a Phase 3 study in which patients in the control arm would receive either sunitinib or sorafenib rather than placebo. Approximately 4 months after the approval of these two medications in the United States, the applicant chose to initiate their Phase 3 placebo-controlled study in treatment-naïve and cytokine pre-treated patients outside the United States.

The relative efficacy of pazopanib to current first-line agents in the treatment of renal cell cancer is unknown. No information is available on the use of pazopanib in patients who have received commonly used first line agents, such as sunitinib or temsirolimus.

Pazopanib was not mutagenic or clastogenic in pre-clinical studies. However, in pre-clinical studies pazopanib impaired female fertility and induced embryo-fetal toxicity. In animals, pazopanib accumulated in the uvea, meninges, skin, and liver and was excreted in the feces. In repeat dose toxicity studies, pazopanib targeted the teeth, growth plate, bone, bone marrow, gastrointestinal tract, liver, and reproductive system. This included bone marrow hypocellularity, growth plate hypertrophy, trabecular atrophy and eosinophilic foci and adenoma in the liver of one species (rodents).

Pazopanib was 14-39% bioavailable with peak absorption at 2-8 hours. It was metabolized by CYP3A4 and to a lesser extent by CYP1A2 and CYP2C8. After administration of radio-labeled pazopanib, 82% of the total radioactivity was eliminated in the feces; 67% was unchanged drug. Metabolites accounted for less <10% of administered drug.

There was a strong food effect associatede with pazopanib. Pazopanib should be taken without food. Drug-drug interaction may occur with other molecules metabolized by CYP3A4, such as lapatinib and enzyme-inducing anti-convulsants. Pazopanib was found to be a substrate of P-glycoprotein. In a pooled pharmacogenetic analysis, variation in the hemachromatosis gene and UGT1A1 were associated with elevations in ALT and bilirubin, respectively.

An exposure-response relationship was not observed between PFS and pazopanib trough concentrations. However, a clear relationship was seen between ALT elevation and the pazopanib trough. Because pazopanib has less than dose proportional PK, to have a

meaningful reduction in exposure, an initial dose reduction of 400 mg was recommended with subsequent reductions in 200 mg increments.

VEG105192 was a Phase 3, double-blind multi-center study in which patients with locally advanced and/or metastatic renal cell carcinoma who were treatment naïve or cytokine pre-treated (1 prior regimen of IL-2 and/or INFα) were randomized 2:1 to pazopanib or placebo. Eligible patients were stratified by performance status, prior nephrectomy, and prior cytokine therapy. Treatment continued until disease progression, death, or unacceptable toxicity. Efficacy assessments were conducted every 6 weeks until week 24 then every 8 weeks.

The primary endpoint, PFS, was evaluated by an independent review committee using the RECIST criteria. In the primary analysis, the interval between the date of randomization and the last adequate assessment was used for patients who were: 1) alive without documented progression; 2) discontinued due to toxicity; 3) who had extensive missing visits ($\geq$ 12 weeks); or 4) who received a new anticancer treatment without documented progression. Major secondary endpoints included overall survival and overall response rate (CR + PR). All efficacy analyses were conducted in the intent-to-treat (ITT) population. Patient demographics were well balanced between arms.

The primary analysis of PFS strongly favored pazopanib. The analysis in Table 1 included only Independent Review Committee (IRC)-determined progression. The IRC and investigator assessments of progression agreed in 66% and 71% of patients. Although the IRC and investigator assessments differed, the number of patients censored by the IRC due to inadequate assessment or with investigator-determined, but not IRC-determined progression was similar (29% vs. 31%) between arms. A sensitivity analysis conducted for patients with missing or inadequate efficacy assessments strongly favored pazopanib. The assessment schedule, every 6 weeks for 24 weeks and then every 8 weeks, may also have contributed to the 5 month difference in the median PFS.

The results of interim analysis of overall survival (OS) were also included in Table1. This interim analysis was performed when approximately 60% of events were available. Patients in the placebo arm were permitted to crossover to pazopanib following disease progression. Given the rate of crossover (70 of 89 eligible patients crossed over from placebo to pazopanib), additional follow up may not demonstrate a statistically significant difference in OS. The overall response rate was also included in the table and was similar to the response rate in the Phase 2 program.

Table 1: Endpoint Analyses

	Placebo N = 145	**Pazopanib N = 290**
Progression Free Survival		
Status n (%)		
Progressed or Died	98 (68%)	148 (51%)
Censored	47 (32%)	142 (49%)
Median Progression Free Survival (95% CI)	4.2 mo (2.8, 4.2)	9.2 mo (7.4, 12.9)
Hazard Ratio (95% CI); p value (stratified logrank)	0.46 (0.34, 0.62); < 0.01	

Overall Survival		
Status n (%)		
Death	67 (46)	109 (38)
Censored	78 (54)	181 (63)
Median Overall Survival (95% CI)	18.7 mo (14.6, 20.1)	21.1 mo (19.3, -)
Hazard Ratio (95% CI); p value (stratified logrank)	0.73 (0.53, 1.0); p = 0.02	
Response Rate		
CR + PR n (%)	5 (3)	88 (30)

Since the Phase 3 study was performed outside the United States, data from the Phase 2 study was used to compare the response rate in patients from the United States (32%) with the response rate from patients outside the U.S. (36%). These response rates were both similar to the response rate of patients on the pazopanib arm of the Phase 3 study.

The evaluation of the safety of pazopanib was based on data from a randomized controlled trial of pazopanib (N = 290) vs. placebo (N = 145); data from patients with renal cell carcinoma exposed to pazopanib (N = 593); and data from patients with other tumor types who received pazopanib alone (N = 397).

In the randomized Phase 3 trial, the median exposure to pazopanib was 7.4 months. In all of the renal cell carcinoma studies, the median duration of exposure was 7.7 months. In the Phase 3 study, dose delay occurred in 43% of pazopanib patients and 10% of control while dose reduction occurred in 37% of pazopanib patients and 6% of control.

The same percentage of patients in the treatment and control arms died due to an adverse event. However, when the causes of death were examined, it was found that only patients in the treatment arm died due to adverse events associated with the inhibition of VEGF, such as hemorrhage or CVA.

There were few grade 3-4 adverse events (AEs) which differed by at least 2% between arms (Table 3). Abnormal hepatic function was the most common disorder. Hypertension and proteinuria have been seen with products that affect the VEGF pathway.

Table 2: Grade 3-4 AEs that Differ by ≥ 2% between Arms in the Phase 3 Study

	Placebo N = 145	**Pazopanib N = 290**
Any Grade 3-4 Event	33 (22.8%)	131 (45.2%)
Gastrointestinal Disorders		
Diarrhea	1 (0.7%)	13 (4.5%)
Hepatobiliary Disorders		
Hepatic Function Abnormal[1]	3 (2.1%)	39 (13.4%)
Renal and Urinary Disorders		
Proteinuria	0	6 (2.1%)
Vascular Disorders		
Hypertension	1 (0.7%)	13 (4.5%)

[1]Includes the terms ALT increased, AST increased, bilirubin increased, hepatic enzyme increased, hepatic function abnormal, hepatotoxicity, hyperbilirubinemia, and transaminases increased.

Adverse events with a frequency of ≥ 20% in the pazopanib arm of the Phase 3 study are shown in Table 3. These included gastrointestinal events and fatigue. The adverse event profile in all patient with renal cell carcinoma exposed to pazopanib was similar to that in the Phase 3 study. Further, the adverse event profile of patients in the Phase 2 study VEG102616 was similar in the U.S. and non-U.S. patients.

Table 3: Grade 1-4 AEs in ≥ 20% of Pazopanib Treated Patients in the Phase 3 Study

Adverse Event	Placebo N = 145		Pazopanib N = 290	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhea	13 (9%)	1 (<1%)	152 (52%)	13 (5%)
Hypertension	16 (11%)	1 (<1%)	116 (40%)	14 (5%)
Hair Color Change	5 (3%)	0	109 (38%)	1 (<1%)
Nausea/Vomiting	23 (16%)	3 (2%)	104 (36%)	8 (3%)
Abdominal Pain/Discomfort	12 (9%)	2 (1%)	63 (21%)	9 (3%)
Fatigue	13 (9%)	4 (2%)	57 (20%)	7 (2%)

Hypertension has been reported in agents that act through the VEGF pathway. Because of this, vital signs were examined in the 586 patients with renal cell carcinoma exposed to pazopanib. At some point in the study, a diastolic blood pressure > 100 was found in 98 (16.7%) patients, 15 had a diastolic pressure > 110. A systolic blood pressure > 150 was found in 241 (41.1%) patients, 23 had a systolic pressure > 180 at some point during the study. One patient in the renal cell population had a hypertensive crisis and hypertension tended to occur in the first 6 months on study. These findings were consistent with other agents of this class.

Declines in left ventricular ejection fraction (LVEF) have been reported with other tyrosine kinase inhibitors. The applicant monitored LVEF in a study of patients with advanced cervical cancer (Study VEG105281). A safety signal was not seen. However, the median exposure to pazopanib in this study (2.9 months) was less than half that seen in the Phase 3 study of patients with renal cell cancer (7.4 months).

Patients in the pazopanib monotherapy population who met the criteria for Hy's Law are discussed in detail in the medical reviews**. Please refer to this discussion in the medical officer's review for an in-depth discussion of hepatic toxicity.**

An Advisory Committee meeting was held October 5, 2009. The Advisory Committee 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. Most committee members expressed concern about the safety profile of pazopanib, but felt that it was consistent with that of other products used to treat renal cell carcinoma.

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

Hepatotoxicity was included as a boxed warning in the pazopanib label. A Medication Guide will be issued to patients with prescription. The boxed warning and medication guide were included to better inform practitioners and patients about the risks of pazopanib. Please see final, issued label for pazopanib.

Office Recommended Regulatory Action: <u>Regular Approval</u>

Risk Benefit Assessment: Pazopanib has shown a 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. 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. Pazopanib has shown a statistically significant, 5 month improvement in PFS in patients with metastatic or locally advanced renal cell carcinoma. Pazopanib has shown a numerically, but not statistically significant improvement in overall survival.

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/s/

RICHARD PAZDUR
10/19/2009