CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 10, 2009
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
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

1. Introduction

GlaxoSmithKline (GSK) submitted a New Drug Application for pazopanib for the indication:

- Treatment of patients with advanced renal cell cancer.

The key study in this application was a single Phase 3 trial which examined progression free survival 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).

2. Background

Pazopanib was identified as a multi-kinase inhibitor. This included inhibition of the vascular endothelial growth factor receptor (VEGFR). Given the activity of other VEGFR inhibitors in renal cell carcinoma, GSK's first application targeted patients with renal cell carcinoma.

The table below was designed to provide an overview of recently approved products for the treatment of renal cell carcinoma. Note that the majority of these were based on an improvement in progression-free survival (PFS). In renal cell carcinoma, an improvement in PFS is seen as conferring a clinical benefit and regular approvals have been issued based on PFS.

Table 1: FDA-Approved Targeted Therapy for Treatment of Renal Cell Carcinoma

Product Name Approval	Trial Type Patient Population	Primary Endpoint	Key Findings
Sorafenib December 2005 Regular Approval	Randomized, double-blind comparison to placebo in patients with advanced RCC after one systemic therapy	PFS	HR: 0.44 (0.35-0.55) Median PFS 5.5 vs. 2.8 months with placebo
Sunitinib January 2006 Accelerated Approval	Two single arm Phase 2 studies in patients with cytokine-refractory RCC	RR	34.0%; 36.5%
February 2007 Regular Approval	Randomized, double-blind comparison to IFNα in patients with treatment-naive advanced RCC	PFS	HR: 0.42 (0.32-0.54) Median PFS 10.8 vs. 5.1 months with IFNα
Temsirolimus May 2007 Regular Approval	Randomized, open-label comparison to IFNα, in treatment-naive patients with advanced RCC with ≥3 of the 6 negative prognostic risk factors	OS	HR: 0.73 (0.58-0.92) Median OS 10.9 vs. 7.3 months with IFNα
Everolimus March 2009 Regular Approval	Randomized, double-blind comparison to placebo in patients with RCC whose disease progressed after treatment with sorafenib, sunitinib, or both	PFS	HR: 0.33 (0.25-0.43) Median PFS 4.9 vs. 1.9 months with placebo
Bevacizumab July 2009 Regular Approval	Randomized, double- blind comparison of bevacizumab + IFNα to IFNα alone in patients with RCC post-nephrectomy	PFS	HR: 0.60 (0.49-0.72) Median PFS 10.2 vs. 5.4 months with IFNα alone

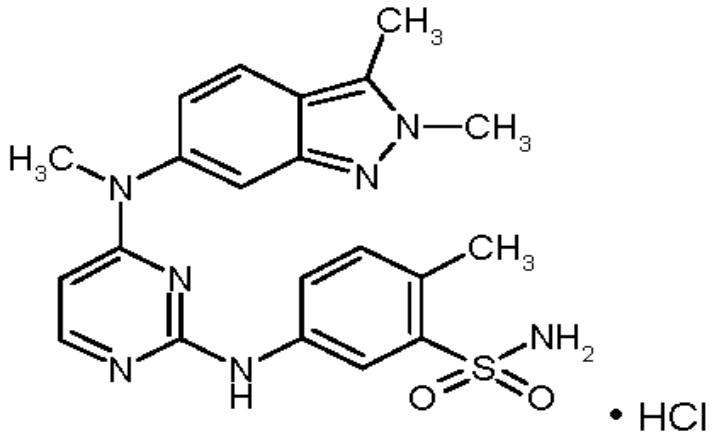
*All the products received regular approval except for sunitinib, which received accelerated approval in December 2006, followed by the conversion to regular approval in February 2007.
PFS: Progression-free survival; RR: Response rate; OS: Overall survival

In the face of these approvals, the applicant was advised to conduct a Phase 3 study in which patients in the control arm would receive sunitinib or sorafenib. However, approximately 4 months after the approval of these two medications in the United States, the applicant chose to begin their Phase 3 placebo-controlled study in treatment-naïve and cytokine pre-treated patients outside the United States. During the Phase 3 discussions, the Agency also cautioned that the acceptability of progression free survival would depend on the magnitude of the difference between arms and the risk benefit profile of their product.

The relative efficacy of pazopanib compared to current first line agents in the treatment of renal cell cancer is unknown. In addition, no information is available on the use of pazopanib in patients who have received the more commonly used first line agents such as sunitinib or temsirolimus. Since sunitinib, sorafenib, and pazopanib work through the same cellular pathway, it is unclear whether resistance to one of these agents will confer resistance to other agents in this class. Di Lorenzo et al administered sorafenib to 52 patients who had previously received sunitinib. Partial response was seen in 9.6% of patients and median time to progression was 16 weeks (JCO 2009 Epub). This response rate was higher than that reported in the product label, 2% while the time to progression appeared to be shorter. Rini et al found that administration of axitinib (an investigational new drug thought to inhibit the vascular endothelial growth factor receptor) in patients with sorafenib-refractory renal cell carcinoma resulted in a response rate of 22.6% and a median PFS of 7.4 months (JCO 2009 Epub).

3. CMC/Device

Pazopanib is a new molecular entity with the formula $C_{21}H_{23}N_7O_2S$•HCl.



Its structure is shown. The applicant has provided batch analysis data for three drug substance production-scale batches manufactured using the proposed commercial process at the commercial site and tested using the commercial methods. In these batches, the pazopanib drug substance was in crystalline form and the manufacturing process involved (b) (4) The applicant has used a quality by design approach to the manufacturing process and this has led to unexpected difficulties. These difficulties have been addressed by the product reviewers and they have recommended product approval.

4. Nonclinical Pharmacology/Toxicology

Pazopanib was not mutagenic or clastogenic. 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).

5. Clinical Pharmacology/Biopharmaceutics

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 and 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 also found to be a substrate of P-glycoprotein. Finally, 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 seen 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. Given these findings the clinical pharmacology group has recommended that the applicant optimize their dosing regimen.

6. Clinical Microbiology

There were no microbiology issues.

7. Clinical/Statistical- Efficacy

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 (≥ 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. Table 2 shows the patient's baseline disease characteristics. Most patients underwent prior nephrectomy and slightly more than half received no prior cytokine therapy. Few patients in either group were in the MSKCC poor risk category.

Table 2: Baseline Disease Characteristics

Parameter	Placebo N = 145	Pazopanib N = 290
Prior Surgery		
Nephrectomy	127 (88%)	258 (89%)
Other	14 (10%)	20 (7%)
Prior Therapy		
Cytokine	67 (46%)	135 (47%)
None (treatment-naïve)	78 (54%)	155 (53%)
MSKCC Risk Factors*		
0 (Favorable)	57 (39%)	113 (39%)
1-2 (Intermediate)	77 (53%)	159 (55%)
≥3 (Poor)	5 (3%)	9 (3%)
* The 5 risk factors were performance status <80%, a low hemoglobin, an elevated LDH, an elevated corrected calcium, and no prior nephrectomy.		

Efficacy Results of VEG105192

The primary analysis of PFS strongly favored pazopanib. The analysis in Table 3 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. Further, 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 Table 3. 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 3: 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.

8. Safety

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.

Deaths

Table 4 provides information on the causes of death, other than disease progression in the Phase 3 study. 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. An unexpected finding was the diagnosis of gastric cancer in 2 patients during the study period. They were diagnosed 125 days and ~ 1 year after the initiation of pazopanib. One of the patients was found to have peritoneal carcinomatosis due to a mucinous adenocarcinoma and it is unclear whether the patient's initial presentation was due to gastric cancer. The observed vs. expected rate of gastric cancer using SEER data

(these patients were outside the U.S. and living in countries with a higher incidence of gastric cancer) is 1 vs. 0.3 for males and 1 vs. 0.14 for females. There is no reported association between renal cell and gastric cancer. Papers from countries with a high incidence of gastric cancer have reported renal cell carcinoma in a minority of these patients.

Table 4: Patient Deaths in the Phase 3 Trial

	Placebo N = 145	**Pazopanib N = 290**
All Deaths	76 (52.4%)	147 (51.0%)
Progressive Disease	66	129
Adverse Event	10 (7.0%)	20 (7.0%)
Probable Progressive Disease	4	2
Sudden Death	2	2
Unknown	1	3
CVA	0	3
Pneumonia	2	1
Cardiac Failure	1	1
Gastric Cancer	0	2
GI Hemorrhage	0	2
Hemoptysis	0	2
Bowel Perforation	0	1
Myocardial Infarction	0	1

Discontinuations

In the 120 day safety update, the applicant did not provide a complete disposition dataset for the randomized Phase 3 study. In separate datasets, information was available for patients who discontinued due to an adverse event, were lost to follow up, or had made a decision to withdraw. Of note, patient 116 discontinued study drug due to grade 1 facial edema, thought by the investigator to be drug related.

The patients in the pazopanib arm who were lost to follow up or decided to withdraw were further evaluated to determine if any of these patients had an adverse event just prior to their discontinuation date. Two patients who were lost to follow up developed paraplegia prior to discontinuation and one patient had a fractured limb. It is unclear why these patients were not included in the category disease progression. Three patients included in the categories lost to follow up or patient decision had an adverse event shortly before discontinuation (cardiac arrest, hepatotoxicity, and diarrhea/fatigue).

Table 5: Patient Discontinuations in the Phase 3 Trial

	Placebo N = 145	**Pazopanib N = 290**
Discontinuations		
Lost to Follow Up	3	12
Patient Decision	2	11
Adverse Event n (%)	7 (4.8%)	46 (15.9%)
Blood and Lymphatic Disorders	1	1
Cardiac Disorders	0	5
Gastrointestinal Disorders	0	10
General Disorders	2	6
Hepatobiliary Disorders		
Hepatic Function Abnormal[1]	1	11
Infections and Infestations	0	1
Investigations	1	1
Metabolism and Nutrition	0	2
Musculoskeletal Disorders	2	2
Neoplasms	0	2
Nervous System Disorders	1	3
Psychiatric Disorders	0	2
Renal and Urinary Disorders	0	4
Skin Disorders	0	1
Vascular Disorders	0	2

[1] Includes the terms hyperbilirubinemia, ALT increased, AST increased, hepatotoxicity, hepatic enzyme increased.

Grade 3-4 Adverse Events

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

Table 6: 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.

Common Adverse Events

Adverse events with a frequency of ≥ 20% in the pazopanib arm of the Phase 3 study are shown in Table 7. These included gastrointestinal events and fatigue. The adverse event

profile in all patient with renal cell carcinoma exposed to pazopanib (Table 8) 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 7: 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%)

Table 8: Grade 1-4 AEs in ≥ 20% of All Patients with Renal Cell Cancer

Adverse Event	Pazopanib N=593		
	All Grades	Grade 3	Grade 4
Diarrhea	55%	4%	<1%
Hypertension	41%	6%	0
Hair Color Change	40%	<1%	0
Nausea	32%	<1%	0
Fatigue	29%	4%	0
Anorexia	24%	2%	0
Vomiting	21%	2%	<1%

The grade 1-4 laboratory abnormalities in the Phase 3 study are shown in Table 9. The frequency of Grade 3/4 elevations in ALT/AST was markedly different between arms. A decrease in hematologic parameters was also seen with pazopanib, but there were few grade 3-4 events. Laboratory chemistries for all patients with renal cell carcinoma exposed to pazopanib are provided in Table 10. Table 10 includes additional laboratory abnormalities such as hyponatremia and hypocalcemia which are not seen in the Phase 3 study. This was thought to be due to the accrual of patients with more advanced disease in the Phase 2 program.

Table 9: Grade 1-4 Laboratories in ≥ 30% of Patients in the Phase 3 Study

	Placebo N = 145			Pazopanib N = 290		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
ALT/AST	47 (32%)	2 (1%)	0	195 (67%)	36 (12%)	5 (2%)
Hyponatremia	43 (30%)	8 (4%)	0	105 (36%)	14 (5%)	4 (2%)
Hypophosphatemia	24 (16%)	2 (1%)	0	103 (36%)	13 (5%)	0
Hypomagnesemia	37 (25%)	0	0	88 (30%)	2 (1%)	4 (2%)
Anemia	88 (26%)	2 (1%)	1 (<1%)	156 (55%)	5 (2%)	2 (1%)
Neutropenia	13 (9%)	0	0	105 (36%)	4 (2%)	1 (<1%)
Thrombocytopenia	13 (9%)	0	1 (<1%)	103 (35%)	4 (2%)	1 (<1%)

Table 10: Laboratory Abnormalities in ≥ 30% of All Patients with Renal Cell Cancer

	Pazopanib N = 593		
	All Grades	**Grade 3**	**Grade 4**
ALT	52%	9%	1%
AST	54%	6%	<1%
Hyperglycemia	48%	2%	0
Bilirubin (total)	36%	2%	<1%
Hypophosphatemia	36%	4%	0
Hyponatremia	35%	6%	<1%
Hypocalcemia	34%	1%	<1%

Significant Adverse Events

Table 11 lists a series of important adverse events observed on the randomized Phase 3 trial. These events occurred throughout the treatment period. They have been seen, to various degrees, with other agents that act through the VEGF pathway. Note, however, that some of these events (i.e., hand foot syndrome or torsades) while seen with other VEGF receptor tyrosine kinase inhibitors do not appear to be directly related to suppression of VEGF. While the incidence of each of these events was low, when taken as a whole, they represented a substantial risk. The incidence of these events in the randomized trial was similar to that in the renal cell carcinoma population (N = 593).

Table 11: Important Adverse Events in the Phase 3 Trial

Adverse Event	**Placebo N = 145**		**Pazopanib N = 290**	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Hemorrhage	8 (6%)	0	32 (11%)	7 (2%)
MI/Ischemia	0	0	8 (3%)	6 (2%)
CVA/TIA	0	0	5 (2%)	3 (1%)
Fistula/Perforation	0	0	3 (1%)	2 (1%)
Hand-Foot Syndrome	1 (<1%)	0	16 (6%)	2 (1%)
Proteinuria	0	0	29 (10%)	6 (2%)
QTc Prolongation	18 (13%)[1]	0	50 (18%)[2]	3 (1%)
Torsades de Pointes	0	0	1 (0.3%)	1 (0.3%)

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).

Hepatic Toxicity

The table below shows the number of patients in the pazopanib monotherapy population who met the criteria for Hy's Law as discussed in "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation." Identification of these patients required that the patient show evidence of hepatic injury (elevated ALT), injury sufficient to affect the synthetic capacity of the liver (elevated bilirubin), and have no other cause of liver injury. The identification of patients meeting the criteria for Hy's Law suggested that drug induced liver injury had occurred and predicted that the rate of hepatic failure would be approximately 1/10 the rate of Hy's Law cases. That is, if 1 patient in 1000 mets the criteria for Hy's Law, the rate of hepatic failure, when the drug is marketed to a larger population, was expected to be 1 in 10,000. The value of Hy's Law in this population is unclear for the following reasons.

- Hy's Law has not been applied to oncology trials.
- Other causes of liver injury must be ruled out.
    - This includes the exclusion of patients with an elevated alkaline phosphatase. This is reasonable in otherwise healthy patients. However, in patients with advanced cancer, elevations in alkaline phosphatase elevation may be due to boney metastases rather than cholestasis.
    - This includes the exclusion of patients receiving acetaminophen or other medications known to cause liver injury. This is reasonable in otherwise healthy patients. However, few patients with advanced cancer are on few or no other medications.
- Hepatic failure is predicted to occur at ~ 1/10 the rate of Hy's Law cases. However, in patients with advanced cancer, lesser degrees of liver dysfunction may interact with their co-morbid conditions to increase the rate of hepatic failure and death.

Four of 984 (0.4%) patients in the pazopanib monotherapy population met the criteria for Hy's Law. This included patients 152, 170, 386, and 410. FDA review identified two patients who died with hepatic failure, patients 233 and 386.

Pazopanib itself cause an elevation in bilirubin and patients 170 and 223 were heterozygous for UGT1A1. Therefore, the bilirubin values for the 4 Hy's Law cases as well as the 2 patients who died with hepatic failure are shown below (N=5).

- Patient 152 had a maximum total bilirubin of 56.6 µmol/L (nml 0-17) with a direct bilirubin of 25 µmol/L (nml 0-3.4).
- Patient 170 had a maximum total bilirubin of 58.14 µmol/L (nml 0-17.1). Direct and indirect bilirubin was not measured.
- Patient 233 had a maximum total bilirubin of 39.33 µmol/L (nml 5.13-20.52). Direct bilirubin 3 days later was 42.75 µmol/L (nml 0-3.42).
- Patient 386 had a maximum total bilirubin of 62 µmol/L (nml 5-17) with a direct bilirubin of 17 µmol/L (nml 0-10).

- Patients 410 had a maximum total bilirubin of 45.579 μmol/L (nml 3.42-17.1). Direct and indirect bilirubin was not measured.

These values were not consistent with elevations due to heterozygosity of UGT1A1 or enzyme inhibition. Elevations in total bilirubin up to 5 mg/dL may be explained by Gilbert's syndrome (p. 1321, Harrison's Principles of Internal Medicine 11th Edition). However, the presence of more marked elevations suggested an additional cause for these elevations.

There have been deaths in association with hepatic failure. Patients 233 and 386 became ill on days 9 and 28 of pazopanib and both died just 4 days after the initial illness, on days 13 and 32, respectively. Patient 170 developed elevated liver tests in association with pazopanib. These normalized, but increased following rechallenge with pazopanib. The patient died of hemoptysis in with ongoing hepatic dysfunction. Finally, in the hospital autopsy report of patient 121 (on pazopanib and topotecan), the cause of death was ruled to be drug induced liver injury. Patients 121 and 170 are not included in Table 13.

The applicant has identified patients 121 (not in the monotherapy population), 233, 386, and 912 as consistent with Hy's Law.

Table 12: Hepatic Laboratory Abnormalities in the Pazopanib Monotherapy Studies

	Pazopanib N = 984
ALT > 3xULN	145
ALT > 10xULN	28
Bilirubin > 2xULN	46
ALT ≥ 3xULN and Bilirubin ≥ 2xULN	12
ALT ≥ 3xULN, Bilirubin ≥ 2xULN and AKP ≤ 2xULN	4

While deaths have occurred in association with hepatic failure, the majority of patients with elevated LFTs adapt to pazopanib. The table below provides an overview of the number of patients with a grade 3-4 ALT in the Phase 3 study and the outcomes of these patients. Most abnormalities occurred within the first 6 weeks of treatment with > 90% by week 18. Ninety-two percent (92%) of patients on the Phase 3 study recovered with a reduction to grade 0-2 ALT. Most patients recovered following dose interruption or discontinuation, but 39% did so without a reduction in pazopanib.

Table 13: Grade 3-4 ALT Abnormalities in the Phase 3 Study

Parameter	Grade 3-4 ALT N = 36
Timing of Occurrence	
≤ 6 Weeks After Initiation	72%
> 6 Weeks After Initiation	28%
Dose Modification	
Interruption	55%
Reduction	55%
Neither	39%
Recovery (Grade 0-2)	92%
Death Associated with Hepatic Insufficiency	2 Patients

The applicant has described risk factors for the development of an ALT > 3xULN. Elevations in ALT may be related to dose, ALT at week 4, age > 60, and female sex. The applicant also noted that baseline bilirubin and the change from baseline at the first assessment are predictors for a rise in ALT. These suggest some strategies for mitigation of the risk of elevations in ALT. Monitoring of liver function tests has been recommended in the product label.

Thyroid Dysfunction

Thyroid dysfunction has been seen with other drugs of this class. The applicant, therefore, prospectively examined the effect of pazopanib on thyroid function. Elevations in TSH were more common in the pazopanib arm than with placebo (TSH > 5 mU/L: 32% vs. 8%). However, the increase in TSH was accompanied by a decrease in T4 in a small number of patients, 4% in the pazopanib and < 1% in the placebo arm. Hyperthyroidism was seen in 2% of patients in the pazopanib and 1% of patients in the placebo arm.

9. Advisory Committee Meeting

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.

10. Pediatrics

Since renal cell carcinoma is rarely seen in pediatric patients, the applicant was granted a waiver by the Pediatric Review and Evaluation Committee. The applicant is not required to conduct pediatric studies.

11. Other Relevant Regulatory Issues

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.

12. Labeling

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.

13. Recommendations/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.

- Recommended Comments to Applicant: See post-marketing requirement above.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22465	ORIG-1	GLAXO WELLCOME MANUFACTURING PTE LTD DBA GLAXOSMITHKLINE	VOTRIENT TABLETS

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/s/

VIRGINIA E MAHER
10/13/2009