

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-465**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Office of Surveillance and Epidemiology  
Division of Epidemiology  
Team Leader Memo

Date: October 16, 2009

To: Solomon Iyasu, M.D., M.P.H.  
Director,  
Division of Epidemiology  
Office of Surveillance and Epidemiology (OSE)

From: Gwen Zornberg, M.D., Sc.D.  
Team Leader,  
Division of Epidemiology  
Office of Surveillance and Epidemiology (OSE)

Subject: Covering memorandum for Syed Rizwanuddin Ahmad, M.D.  
M.P.H., F.I.S.P.E., F.C.P. memorandum on Pazopanib dated  
October 16, 2009

Drug Name: Pazopanib (Votrient) Tablet/200mg and 400 mg

Proposed Indication: Treatment of patients with advanced renal cell carcinoma (RCC)

Applicant: GlaxoSmithKline

OSE RCM#: 2009-1560

**Background**

This is written as a cover memorandum to the memorandum by Dr. Syed Rizwanuddin Ahmad M.D., M.P.H., F.I.S.P.E. on pazopanib dated October 16, 2009. Dr. Ahmad's memorandum does not include a full evaluation of the safety and efficacy data in the context of expected survival of the patients in the pazopanib development program, nor an evaluation of the nonclinical and clinical data pertaining to major safety concerns.

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 10-0 that the benefit to risk profile was acceptable. Dr. Ahmad referred to this meeting in his review.

In his review, hepatic toxicity that has received the most attention in Dr. Ahmad's attention with less attention given to other areas of concern such as hemorrhage, MI/Ischemia, CVA/TIA, fistula/perforation, Torsades de Pointes or QTc prolongation. Dr. Maher, in the CDTL review dated October 13, 2009, noted a number of issues to frame the rate of 0.04% of patients with Hy's Law case in the pazopanib database. She stated that the value of the Hy's Law cases is unclear because Hy's Law has not been applied to oncology trials, this includes patients with elevated alkaline phosphatase that may be secondary to boney metastases rather than cholestasis; those receiving acetaminophen; and the clinical observation that in patients with advanced cancer, lesser degrees of liver dysfunction may interact with comorbid conditions to increase rates of hepatic failure and death. Dr. Maher also noted that other drugs in this class of tyrosine kinase inhibitors are associated with adverse experiences such as declines in LVEF. The sponsor monitored LVEF in a study of patients with advanced cervical carcinoma and a safety signal was not observed.

#### **Sponsor's postmarketing risk assessment proposal**

Dr. Ahmad commented on the Sponsor's postmarketing risk assessment proposal. In general, I share his concern regarding the limitations of the (b) (4) database proposed by the applicant that does not include patients older than 65 years. RCC generally affects people in the 50 to 70 year age range. Individuals at the higher end of the age range tend to be the most vulnerable to adverse drug experiences. Hence, the safety profile should be characterized across the entire age range, including patients over 65 years. The truncation at age 65 makes the (b) (4) database inadequate for a study. The (b) (4) database proposed by the sponsor poses additional challenges that could potentially be compensated for by adding more intensive measures to follow up on safety events that occur outside of the offices where the data is more easily gathered. The loss of data on acute hepatic emergencies outside of the oncology offices that appears to be the major limitation (b) (4) database would also need to be remedied. I think that an epidemiological study carried out in cancer centers affiliated has the potential to be an informative approach, given the database options following introduction to market.

Dr. Ahmad's memorandum contains his specific opinions and he recommends consideration of a mandatory patient registry as an option for the sponsor's risk assessment proposal. This recommendation of a mandatory patient registry is not the opinion of OSE. The term "mandatory" implies the need to implement a REMS for this treatment of advanced cancer suggests much greater toxicity of pazopanib compared to the 5 drugs on the market with similar mechanisms of action where no mandatory registry has been required. Requiring patients to participate in a mandatory registry for the

purposes of conducting a study may be unethical and contrary to federal regulations governing the protection of human subjects. Participation in a study should always be voluntary. A mandatory registry to protect patient safety or mitigate known serious drug risks is an option if the safety issue justifies deployment of such a restricted program. Dr. Ahmad's memorandum does not provide a benefit risk analysis with risk mitigation elements that would justify a mandatory registry with restricted distribution. In terms of scientific information to be garnered from a registry study, the information would be limited. At best, the registry would likely estimate the upper bound of the incidence rate of SAEs such as hepatotoxicity.

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/s/  
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GWEN L ZORNBERG  
10/19/2009



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: October 16, 2009

To: Robert Justice, M.D., Director  
Division Of Drug Oncology Products (DDOP), HFD-560

Through: Solomon Iyasu, M.D., M.P.H., Director  
Division of Epidemiology

Through: Gwen Zornberg, M.D., Sc.D., Team Leader  
Division of Epidemiology

From: Syed Rizwanuddin Ahmad, M.D., M.P.H., F.I.S.P.E., F.C.P.  
Medical Epidemiologist  
Division of Epidemiology  
Office of Surveillance and Epidemiology

Subject: Evaluation of Sponsor's Plan to Monitor Hepatotoxicity

Drug Name: Drug:  
Votrient® (Pazopanib)

Submission Number: N/A

Application Type/Number: NDA 022-465  
Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2009-1560

## EXECUTIVE SUMMARY

Pazopanib is a new drug that is currently being proposed for the treatment of patients with advanced renal cell carcinoma, a condition for which 5 drugs are already approved. The Division of Drug Oncology Products (DDOP) contacted OSE to review the sponsor's plan to use healthcare claims databases to monitor postmarketing safety of the drug, (b) (4)

[REDACTED]

[REDACTED]

The risk management plan (RMP) as currently submitted by the sponsor has limited information and is inadequate for a full evaluation of its value. Additionally, the inability of the proposed databases to capture elderly population is problematic since RCC usually affects people in the age range of 50-70 years. A different epidemiological study design is recommended. The sponsor should submit an in-depth epidemiologic study protocol before initiation which should describe the study population, delineate the methods to measure exposure, as well as the inclusion and exclusion criteria. In terms of the major safety outcomes to be evaluated, the specific ICD-9 codes and ascertainment that will be used should be clearly presented, as well as method of diagnostic validation. For example, there are no ICD-9 codes for *torsades de pointes* and it is not clear how the sponsor plans to capture treatment emergent *torsades de pointes*. The protocol must provide the sample size and power calculations to detect the safety outcomes under evaluation and the hypotheses being tested in the statistical analysis plan. If pazopanib is approved, we recommend that data collection be initiated soon after market introduction rather than with the 18 months lag proposed by the sponsor. This has the potential to expedite the development of more targeted preventive efforts to mitigate the potential occurrence of hepatotoxicity and other major safety concerns.

If pazopanib is approved based on the available data, we believe the proposed risk management plan submitted by the sponsor is inadequate. A more comprehensive option for the assessment of postmarketing safety data would be the conduct of a prospective, epidemiological study in collaboration with major academic cancer centers in the U.S. Alternatively, the use of a mandatory patient registry could be considered.

## 1. INTRODUCTION

Pazopanib is a new tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-alpha and -beta, and c-kit tyrosine kinases. It has been developed for the treatment of various malignancies but is currently being proposed for the treatment of patients with advanced renal cell carcinoma. Since 2005, FDA has approved five products for the treatment of advanced renal cell carcinoma (RCC) including sorafenib and sunitinib which have similar mechanism of action. All these products are administered orally.

In the regulatory history of pazopanib, it is important to highlight that in March 2006, the FDA expressed its concern and advised the sponsor to conduct a Phase 3 study with pazopanib in which control patients should receive either sorafenib, sunitinib, or a cytokine. The sponsor did not follow the Agency's advise and began their Phase-3 placebo-controlled study outside the U.S. This Phase 3 study was primarily conducted in developing countries including Poland, Argentina, Chile, Lithuania, Slovakia, Russia, Pakistan, and Korea, where patients may have different natural history of the disease, standard of care, and ethical and technical standards in the conduct of clinical trials may be different. This Phase 3 study showed a 5 month improvement in median PFS (progression free survival) without a statistically significant improvement of overall survival. This Phase 3 study is the key study in the NDA package of pazopanib.

An evaluation of clinical trials submitted in support of the proposed indication of pazopanib for RCC suggested that the drug may be associated with an increased risk of hepatotoxicity. A total of 593 patients received at least one dose of pazopanib in the trials for RCC. A higher incidence of serum aminotransferase elevations was noted in the pazopanib arm compared to the placebo arm. Per the FDA briefing document, the majority of the elevations occurred within the first 12 weeks of treatment. The rate of  $\geq$  Grade 3 ALT elevation, defined as  $> 5.0 \times \text{ULN}$  was 13 % in the pazopanib arm compared to 1% in the placebo arm. Similarly the rate of  $>$  Grade 2 ALT elevation, defined as  $> 2.5 \times \text{ULN}$  was 10% in the pazopanib arm compared to 2% in the placebo

arm. In the pazopanib monotherapy population (N=990) four cases of Hy's law were identified and all these cases were from RCC studies (N=593). Hy's law applies to well-documented cases of drug injury that is hepatocellular in nature with clinically evident jaundice.<sup>1</sup> Hy's Law is defined as a concurrent elevation of ALT > 3 x ULN and bilirubin > 2 x ULN. Hy's law signifies serious liver injury with an estimated mortality of about 10%. Two deaths (one of the four Hy's Law cases) associated with hepatic failure were probably related to pazopanib. In the two death cases, the time to onset of hepatic abnormality was 9 and 28 days after drug administration; the time of death from the onset of hepatic abnormality was 4 days. Another hepatic death was identified in a combination study and this was considered probably related to pazopanib by both the FDA reviewers and the sponsor. Pazopanib stands out with respect to its association with serious and fatal hepatotoxicity observed in the pre-marketing setting compared to currently approved drugs for RCC.

In the case of non-oncology drugs, presence of 1-2 Hy's Law cases per 1000 subjects has led to non-approval decision by the FDA. Appropriate interpretation and application of Hy's Law criterion in the oncology setting is unknown given the nature of the disease and limited treatment options.

Like other anti-VEGF or anti-VEGF receptor products, pazopanib is also associated with other life-threatening adverse events such as hemorrhage, arterial thromboembolic events, hypertensive crisis, *torsades de pointes*, hand-foot syndrome, and gastrointestinal fistula/perforation.

Based on the concern that the sponsor's plan to use commercial insurance claims databases that excludes patients older than 65 years which would skew adverse event reporting and that database review will not be conducted until at least 18 months post approval, the Division of Drug Oncology Products (DDOP) contacted OSE to review the sponsor's plan. [REDACTED] (b) (4);

[REDACTED] (b) (4)

DDOP is also interested to know about other better options for postmarketing safety data collection.

## 2. MATERIALS REVIEWED

Materials for this review included

1. Module 1.16 Risk Management Plan UM2008/00411/00 submitted by the sponsor.  
(b) (4) monitoring plan for LFT elevations. Prepared by the sponsor for their meeting with FDA on July 6, 2009.
3. Draft Pazopanib Label.
4. FDA briefing document on pazopanib for the Oncologic Drugs Advisory Committee meeting on October 5, 2009.
5. Cross-Discipline Team Leader Review by V. Ellen Maher, M.D., DDOP, October 13, 2009.
6. Clinical Review by Y. M. Ning, M.D., Ph.D., I. Waxman, and V. Ellen Maher, M.D., DDOP, October 6, 2009.

## 3. REVIEWER'S COMMENTS

In the Module 1.16 Risk Management Plan (RMP), the sponsor states that it is planning to monitor the safety profile of pazopanib, including hepatotoxicity, ischemic events (myocardial infarction, cerebrovascular accident, and transient ischemic attack), and *torsades de pointes* (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

The Risk Management Plan (RPM) states that the adverse drug event association will be captured using ICD-9 diagnoses codes present in the medical claims data.

### **Monitoring for Cardiovascular Disease Adverse Events**

For cardiovascular disease (CVD) adverse events, the RPM states that the sponsor plans to compare the rates of each CVD outcome in claims databases with rates observed in the pazopanib clinical trials. In order to ensure adequate sample size of pazopanib users to generate robust estimates, a feasibility component will be added to see if the database has accrued a minimum number of 200 pazopanib users.

*However, no details have been provided as to the study design; methods, the specific ICD-9 codes that will be used; sample size; power considerations; how exposure will be measured; what are the inclusion and exclusion criteria; how outcome will be ascertained and validation will be done; and how the analysis will be done. For example, there are no ICD-9 codes for torsades de pointes and it is not clear how the sponsor plans to capture torsades de pointes. Also, it is not clear how the investigators came up with the 200 number.*

### **Monitoring for Hepatotoxicity**

In addition to the proposed studies in claims databases, the RMP states that the sponsor will use an oncology-specific Electronic Medical Record (EMR) database called the (b) (4) system to monitor hepatotoxicity. The (b) (4) database is a repository of > 185,000 cancer patients from 18 U.S. community oncology practices across 15 states. The RMP states that the proposed monitoring of hepatotoxicity will start after a minimum of 200 pazopanib users have accrued in the (b) (4) database.

*While the (b) (4) database may be a known database in the oncology circle, a search in the National Library of Medicine's PubMed database did not identify any literature which supports the use and acceptability of the (b) (4) system to monitor hepatotoxicity. It is not clear how the sponsor came up with the minimum of 200 pazopanib users when they will initiate hepatotoxicity monitoring. Per the sponsor's (b) (4) database is that events treated outside of the oncology clinic such as 'emergency' acute liver failure cases are likely to be underreported. Such underreporting would likely underestimate the incidence rate of serious hepatotoxicity associated with pazopanib exposure. Moreover the sponsor should come up with a strategy as to how they will capture hepatotoxicity cases outside*

*the specialty community oncology practices. Given that RCC is most common in persons aged 50-70 years and the sponsor is proposing to conduct epidemiologic studies in healthcare claims databases that does not capture the patient population older than 65 years, the sponsor should provide an alternate plan to evaluate a representative sample of patients diagnosed with RCC, particularly patients older than 65 years who are likely to be more susceptible to adverse experiences associated with pazopanib exposure.*

The RMP states that abnormal liver enzyme values from the (b) (4) database will be compared with the abnormal liver enzyme data observed in the pazopanib clinical trials. Abnormal liver enzyme values ( $ALT \geq 5 \times ULN$ ,  $Bili \geq 2 \times ULN$ , and the combination of  $ALT \geq 3 \times ULN$  and  $Bili \geq 2 \times ULN$ ) will be flagged. If the abnormal liver enzyme values reach or exceed 2 x the values observed in the pazopanib trials, an in-depth retrospective cohort study will be initiated. In this safety study, liver enzyme elevations will be compared among users of pazopanib and other drugs already approved for the treatment of renal cell carcinoma namely sunitinib, sorafenib, and temsirolimus.

*The sponsor has proposed to initiate a study if the value of abnormal liver enzymes is greater than the values observed in the pazopanib clinical trials. The sponsor should provide a rationale for their proposed methodology and why the comparison should not be against the standard liver enzyme values. Additionally, the sponsor should specify the database that will be used to conduct an in-depth study across the full age range and submit detailed study protocol. Given the strong evidence of hepatotoxicity in the premarketing clinical trials in association with pazopanib, and the availability of other treatment options, it is possible that the market uptake of pazopanib may be inadequate and hence any epidemiological studies conducted in commercial claims databases may be underpowered to monitor the safety outcomes of interest.*

#### **4. SUMMARY, CONCLUSIONS AND RECOMMENDATIONS**

The pazopanib new drug application is being reviewed for the treatment of patients with advanced RCC, a condition for which the prognosis is generally poor and treatment options are limited to five other drugs currently approved for this indication.

Premarketing evidence of serious hepatotoxicity with pazopanib is very strong compared to the other drugs for RCC according to data presented and discussed at the recently

concluded advisory committee meeting. The relative efficacy of pazopanib in RCC is unknown compared to other approved drugs for this indication (Cross-Discipline Team Leader Review by V. Ellen Maher, M.D., DDOP, October 13, 2009). Available data appears to indicate that, in terms of efficacy, pazopanib may not have any major therapeutic advantage over the existing therapies for RCC, but is associated with a strong hepatotoxicity signal (i.e., 4 Hy's Law cases per approximately 1,000 patients). Two deaths (one of the four Hy's Law cases) associated with hepatic failure were probably related to pazopanib. In the two death cases, the time to onset of hepatic abnormality was 9 and 28 days after drug administration; the time of death from the onset of hepatic abnormality was very rapid – only 4 days. Another hepatic death was identified in a combination study and this was considered probably related to pazopanib by both the FDA reviewers and the sponsor. Pazopanib stands out with respect to its association with serious and fatal hepatotoxicity observed in the pre-marketing setting compared to other approved drugs for RCC.

In the case of non-oncology drugs, presence of 1-2 Hy's Law cases per 1000 subjects has led to non-approval decision by the FDA. Appropriate interpretation and application of Hy's Law criterion in the oncology setting is unknown given the nature of the disease and limited treatment options.

The sponsor's plan [REDACTED] (b) (4); [REDACTED] may not provide us with the relevant data to accurately characterize major safety outcomes of interest in the representative population. Moreover, the sponsor's proposed [REDACTED] (b) (4) lag in data collection is unacceptable since this will delay our ability to characterize the risk profile of pazopanib which is vital in any effort for risk mitigation. The sponsor should provide a detailed explanation for the statistical power calculations in an appropriate database with a representative RCC patient sample that includes patients with RCC of any age treated with pazopanib with the ability to follow patients after treatment to evaluate less acute effects of treatment. The detailed protocol for the proposed epidemiological study should be submitted for review prior to initiation. The sponsor's proposed plan to monitor for liver chemistry abnormalities in the [REDACTED] (b) (4);

(b) database is not likely to be adequate given the rapid onset of liver failure in the clinical trials settings. Since the (b) (4) database lacks the ability to collect data on emergency acute liver failure events treated outside oncology clinics, the sponsor should provide a strategy as to how these cases will be captured as well as how they will conduct follow-up on patients who discontinue pazopanib therapy.

Available evidence suggests that for drugs with rapid onset of hepatotoxicity, liver injury may progress to irreversible hepatic failure within less than a reasonable monitoring interval.<sup>2</sup> Given the rapid onset of liver failure in two cases identified in pazopanib trials, identification of an optimal liver enzyme monitoring interval maybe of paramount importance, if such an interval exist, and this may be accomplished by the conduct of additional safety studies.

Based on the Agency's experience, compliance with laboratory monitoring recommendations with drugs that have been associated with hepatotoxicity have been very poor<sup>3-4</sup>. The low survival rate of patients with advanced RCC in the context of limited therapeutic options in oncology, where the threshold for regulatory actions is different from drugs with milder conditions is a challenge.

In conclusion, if pazopanib is approved based on the available data, this reviewer believes that the sponsor's proposed risk management plan is inadequate. This reviewer recommends that the sponsor provide a more intensive approach to postmarketing pharmacovigilance in a representative patient population. A more comprehensive option for the assessment of postmarketing safety data will be the conduct of a prospective cohort study in collaboration with major academic cancer centers in the U.S. Such an epidemiological study has the potential to collect better quality data guided by oncologic expertise in the patient population diagnosed with advanced RCC including patients older than 65 years who would not be able to be evaluated in the sponsor's proposed healthcare claims databases studies. A prospective cohort study design conducted at oncology centers though expensive and will take several years to complete, would however permit the collection of clinical variables not available in claims databases. Alternatively, the use of a mandatory patient registry could be considered which has the potential to:

1. Help further characterize the hepatotoxicity and other major safety signals.
2. Fully quantify serious hepatotoxicity events in all patient population including patients older than 65 years which will not be captured in the proposed claims databases.
3. Explore the potential value of liver enzyme monitoring in mitigating the serious hepatotoxicity risk associated with this drug. And
4. Provide prescribers with pazopanib as an additional therapeutic option to treat RCC.

One potential downside of a mandatory patient registry is the additional burden on prescribers and patients.

## 5. REFERENCES

1. Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.
2. Senior, JR. Monitoring for hepatotoxicity: what is the predictive value of liver “function” tests? *Clin Pharmacol Ther* 2009;85:331-4.
3. Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ..Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001; 286: 831-3.
4. Willy M, Manda B, Shatin D, Drinkard CR, Graham DJ.. A study of compliance with FDA recommendations for pemoline (Cylert). *J Am Acad Child Adolesc Psychiatry* 2002; 41: 785-90.

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SYED R AHMAD  
10/16/2009

GWEN L ZORNBERG  
10/16/2009

Dr. Ahmad's memorandum contains his specific opinions and he recommends consideration of a mandatory patient registry as an option for the sponsor's risk assessment proposal. This recommendation of a mandatory patient registry is not the opinion of OSE. The term "mandatory" implies the need to implement a REMS for this treatment of advanced cancer suggests much greater toxicity of pazopanib compared to the 5 drugs on the market with similar mechanisms of action where no mandatory registry has been required. Requiring patients to participate in a mandatory registry for the purposes of conducting a study may be unethical and contrary to federal regulations governing the protection of human subjects. Participation in a study should always be voluntary. A mandatory registry to protect patient safety or mitigate known serious drug risks is an option if the safety issue justifies deployment of such a restricted program. Dr. Ahmad's memorandum does not provide a benefit risk analysis with risk mitigation elements that would justify a mandatory registry with restricted distribution. In terms of scientific information to be garnered from a registry study, the information would be limited. At best, the registry would likely estimate the upper bound of the incidence rate of SAEs such as hepatotoxicity. Please refer to the DEPI TL memo

SOLOMON IYASU  
10/16/2009

I concur with the DEPI Team Leader's cover memo and do not support a recommendation for a "mandatory patient registry" as an alternative option for consideration. Similar to the DEPI Team Leader, I am in agreement with Dr. Ahmad's other recommendations for postmarketing safety assessment.



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**  
October 19, 2009

Date:

To:

Robert Justice, M.D., Director  
**Division of Drug Oncology Products (DDOP)**

Through:

Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

From:

Shawna Hutchins, BSN, R.N.  
Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Subject:

Addendum to DRISK Review of Proposed Risk Evaluation  
and Mitigation Strategy (REMS)

Drug Name(s):

VOTRIENT (pazopanib) Tablets

Application  
Type/Number:

NDA 22-465

Applicant/sponsor:

GlaxoSmithKline

OSE RCM #:

2009-311  
2009-1070

**RECOMMENDATIONS:**

DRISK finds the following Proposed REMS (Appendix A) and REMS Supporting Document (Appendix B) acceptable.

## Appendix A: Proposed REMS

### **NDA 022465 VOTRIENT™ (pazopanib) TABLETS** **Drug Class and Formulation: Multi- tyrosine Kinase Inhibitor**

**Glaxo Wellcome Manufacturing Pte Ltd d/b/a GlaxoSmithKline**  
**1 Pioneer Sector 1, Jurong, Singapore, 628413, Singapore**  
**1250 S. Collegeville Road, UP4110, Collegeville, PA 19426**  
**610-917-6823**

#### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

##### **I. GOAL**

The goal of this REMS is to inform patients about the serious risks associated with the use of VOTRIENT (pazopanib).

##### **II. REMS ELEMENTS**

###### **A. Medication Guide**

GlaxoSmithKline will ensure that a Medication Guide is available for distribution to patients with each VOTRIENT (pazopanib) prescription in accordance with 21 CFR 208.24. GlaxoSmithKline will include a statement “*Dispense the Medication Guide, attached or provided separately, to each patient pursuant to Federal law*” on the label of each container or package of VOTRIENT (pazopanib) instructing the authorized dispenser to provide a copy of the Medication Guide each time a prescription of VOTRIENT (pazopanib) is dispensed.

###### **B. Communication Plan**

*A Communication Plan is not required for approval of this REMS.*

###### **C. Elements To Assure Safe Use**

*Elements to Assure Safe Use are not required for approval of this REMS.*

###### **D. Implementation System**

*Because this REMS does not include Elements to Assure Safe Use, an Implementation System is not required for approval of this REMS.*

###### **E. Timetable for Submission of Assessments**

GlaxoSmithKline will submit REMS Assessments to FDA 18 months, three years, and seven years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. GlaxoSmithKline will submit each assessment so it will be received by the FDA on or before the due date.

**Appendix B: REMS Supporting Document**

**REMS SUPPORTING DOCUMENT**

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## 1. BACKGROUND

A REMS is proposed for VOTRIENT™ Tablets (NDA 022465) to inform patients of the potential serious risks associated with Votrient Tablets.

## 2. GOALS

The goal of this REMS is to inform patients about the serious risks associated with the use of Votrient (pazopanib). GSK proposes that this be accomplished by the provision of a Medication Guide that will inform patients of the potential risks associated with the use of Votrient, including the potential risk of hepatotoxicity, and signs of liver problems or other side effects that should be immediately communicated to the patient's healthcare provider. In addition to communicating the potential risks associated with Votrient, the Medication Guide will inform patients about things they should discuss with their health care provider before taking Votrient and important information on how to take Votrient.

## 3. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

### a. Additional Potential Elements

#### i. Medication Guide

As required by Federal law, the dispensing pharmacy is required to include a Medication Guide with each prescription for Votrient.

At the time of introduction, only a single retail presentation (200 mg tablets, bottles of 120) will be commercially available. This presentation is a single unit-of-use container when prescribed at the recommended dose of 800 mg. Due to the potential for dose modification, which would result in division of the single unit-of-use container, four Medication Guides will be affixed to each bottle to account for dispensing of partial containers. This is an effort to ensure that sufficient supply of the Medication Guide is readily available to dispensing pharmacies, even in the event that the single unit-of-use container is divided due to dose modifications.

Each Medication Guide is barcode scanned to ensure that the correct version is being used and that the component is available for attaching to each container.

The label of each container of Votrient tablets will include the following instruction to authorize dispensers to provide a MG to each patient to whom the drug is dispensed: (b) (4)  
Dispense the Medication Guide, attached or provided separately, to each patient pursuant to Federal law."

Because the MG is included as part of the primary package for Votrient, GSK has met the requirements of 21 CFR 208.24 for distribution and dispensing of the Medication Guide.

#### ii. Patient Package Insert

The REMS for Votrient does not include a Patient Package Insert as a Medication Guide is provided.

iii. Communication Plan

A Communication Plan is not required for approval of this REMS.

#### **4. REMS ASSESSMENT PLAN (FOR PRODUCTS APPROVED UNDER A NDA OR BLA)**

- i. A survey of the patients' understanding of the potential serious risks associated with Votrient.

GSK will conduct a survey of patients' understanding of the potential serious risks associated with Votrient. GSK will submit its methodology for these assessment at least 3 months in advance of the planned assessments.

- ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24; and report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address non-compliance.

GSK will conduct the periodic assessments identified above. GSK will submit its methodology for these assessments at least 3 months in advance of the planned assessments.

#### **5. OTHER RELEVANT INFORMATION**

NDA 022465 provides for additional commercial presentations of Votrient (200 mg tablets, bottles of 30 and 90, and 400 mg tablets, bottles of 30 and 60) that will not be commercially available at the time of introduction. These are not unit-of-use presentations and GSK hereby commits to notifying the Agency in writing before introducing these presentations. Should any of these presentations be made available they will have sufficient numbers of Medication Guides affixed to each container.

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

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SHAWNA L HUTCHINS  
10/19/2009

CLAUDIA B KARWOSKI  
10/19/2009  
concur

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF ONCOLOGY DRUG PRODUCTS  
DIVISION OF DRUG ONCOLOGY PRODUCTS

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**NDA #:** NDA 022465  
**Products:** Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg  
**SPONSOR:** GlaxoSmithKline  
**FROM:** Richard Pazdur M.D.  
**DATE:** October 15, 2009

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Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Votrient™ (pazopanib hydrochloride) Tablet to ensure that the benefits of the drug outweigh the risk of death related to hepatotoxicity. In reaching this determination, we considered the following:

- A. The estimated number of patients in the United States with advanced renal cell carcinoma is 57,000. This estimate is based on the SEER 2009 database.
- B. Advanced renal cell cancer is a life-threatening condition.
- C. Votrient™ (pazopanib hydrochloride) Tablet has demonstrated an improvement in progression-free survival in a randomized trial.
- D. Votrient™ (pazopanib hydrochloride) Tablet will be indicated for the treatment of patients with advanced renal cell carcinoma. The median duration of treatment in the clinical studies was 7 months.

E. Serious adverse reactions include hepatotoxicity, bleeding, arterial thrombosis, visceral perforation, and torsades de pointes. Some of these reactions can be fatal. The background incidence of these events was minimal or undetectable in the patients receiving placebo in the randomized study supporting the Votrient™ (pazopanib hydrochloride) Tablet NDA.

F. Votrient™ (pazopanib hydrochloride) Tablet is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Votrient™ (pazopanib hydrochloride) Tablet. FDA has determined that Votrient™ (pazopanib hydrochloride) Tablet poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Votrient™ (pazopanib hydrochloride) Tablet. FDA has determined that Votrient™ (pazopanib hydrochloride) Tablet is a product for which patient labeling could help prevent serious adverse effects, and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Votrient™ (pazopanib hydrochloride) Tablet.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIM J ROBERTSON  
10/16/2009  
Votrient REMS Memo NDA 022465

RICHARD PAZDUR  
10/17/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 16, 2009

To: Robert Justice, M.D., Director  
**Division of Drug Oncology Products (DDOP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

From: Shawna Hutchins, BSN, R.N.  
Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation  
Strategy (REMS)

Drug Name(s): VOTRIENT (pazopanib) Tablets

Application Type/Number: NDA 22-465

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2009-311  
2009-1070

## 1 INTRODUCTION

This memorandum is in response to a request by the Division of Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for VOTRIENT (pazopanib) Tablets. Please send these comments to the Applicant and request a response as soon as possible. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. DRISK's review of the Medication Guide was sent to DDOP under separate cover dated October 02, 2009.

## 2 MATERIAL REVIEWED

- VOTRIENT (pazopanib) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated October 15, 2009
- Proposed VOTRIENT (pazopanib) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on October 15, 2009

## 3 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Sponsor.

It is noted in the REMS Supporting Document that the applicant plans to conduct a survey of patients' understanding of the serious risks associated with the use of VOTRIENT (pazopanib), but does not plan to assess the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24; and report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance. We acknowledge that the initial distribution of VOTRIENT (pazopanib) will be in a single retail presentation (200mg tablets, bottles of 120). However due to the potential for future dose modification which would result in the division of the single unit-of-use container, all assessments in accordance with 21 CFR 208.24 are required as part of this REMS.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### Comments to GlaxoSmithKline:

See the appended VOTRIENT (pazopanib) REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

#### a. GOAL

Revise your goal as follows:

*The goal of this REMS is to inform patients about the serious risks associated with the use of VOTRIENT (pazopanib).*

- b. We acknowledge that the initial distribution of VOTRIENT (pazopanib) will be in a single retail presentation (200mg tablets, bottles of 120). However due to the potential for future dose modification which would result in the division of the single unit-of-use container, we remind you to comply with 21 CFR 208.24:
- Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
    - A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
    - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

We have some editorial comments in this section of the proposed REMS.

- c. The timetable for submission of assessments of 18 months, three years and seven years is acceptable.
- d. Your submission states that assessments (of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24; and a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance) are unnecessary because the products are distributed in unit-of-use packaging that contains the Medication Guide. We acknowledge that the initial distribution of VOTRIENT (pazopanib) will be in a single retail presentation (200mg tablets, bottles of 120). However due to the potential for future dose modification which would result in the division of the single unit-of-use container, the assessments are a required element of this REMS.
- e. Please submit for review a detailed plan to evaluate patients’ understanding about the safe use of VOTRIENT (pazopanib). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded “REMS Correspondence.” If you plan to conduct this assessment using a survey, your submission should include:
- All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of VOTRIENT (pazopanib). This should include, but not be limited to:
    - Sample size and confidence associated with that sample size
    - How the sample will be determined (selection criteria)

- The expected number of patients to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

3 Pages Withheld as b(4) Trade Secret/  
Confidential

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/s/  
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SHAWNA L HUTCHINS  
10/16/2009

CLAUDIA B KARWOSKI  
10/16/2009  
concur