CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-465

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******Pre-decisional Agency Information******

Memorandum

Date: October 13, 2009

To: Kim Robertson, Project Manager, DDOP

From: Stephanie Victor, Regulatory Review Officer, DDMAC

CC: Robert Dean, DTC Group Leader, DDMAC
Keith Olin, Regulatory Review Officer, DDMAC
Catherine Gray, Professional Group Leader, DDMAC

Subject: NDA # 22-465
DDMAC comments for Votrient (pazopanib)
Patient Medication Guide

DDMAC has reviewed the proposed Patient Medication Guide for Votrient (pazopanib) submitted for consult on January 23, 2009, and offers the following comments. Comments regarding the proposed PI were previously provided during a labeling meeting on October 7, 2009 by Keith Olin.

The version of the draft PI and MedGuide used in this review is titled, "GSKs Latest Proposed VOTRIENT Label (2).doc" sent via email on October 7, 2009. This document was last modified on October 6, 2009.

General Comment

DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the patient labeling, please contact Stephanie Victor at 301-796-3693 or Stephanie.Victor@fda.hhs.gov.

25 Pages Withheld as b(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHANIE L VICTOR
10/13/2009

DSI CONSULT: Request for Clinical Inspections

Date: February 18, 2009

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCPB2, DSI

cc: Robert S. K. Young, M.D., GCPB2, DSI

Through: Y. Max Ning, M.D., Clinical Reviewer, DDOP
V. Ellen Maher, MD. Clinical Team Leader, DDOP
Robert L. Justice, M.D., Division Director, DDOP

From: Kim Robertson, Consumer Safety Officer, DDOP

Subject: **Request for Clinical Site Inspections**
NDA 22-465
Sponsor: GlaxoSmithKline
Drug: Votrient® (pazopanib) Tablets of 200 mg or 400 mg for oral administration
NME: Yes
Review: Standard
Study Population: adults with advanced renal cell carcinoma

PDUFA: October 19, 2009
Action Goal Date: September 14, 2009
Inspection Summary Goal Date: August 01, 2009

I. Background Information

Pazopanib is a new multi-target tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, Platelet-derived Growth Factor Receptor (PDGFR)-α and -β, and c-Kit tyrosine kinases. It has been developed for the treatment of patients with advanced renal cell carcinoma (RCC). Products similar to pazopanib in mechanism and clinical indication include sorafenib and sunitinib, which received FDA approval for treatment of RCC in 2005 and 2006, respectively.

In the current NDA, the sponsor provided evidence of the efficacy and safety of pazopanib to support an indication for the treatment of patients with RCC. The evidence is based on the results of a large, randomized, double-blinded Phase 3 study (VEG105192) and a supportive single-arm Phase 2 study (VEG102616). The Phase 3 study serves as the basis for the regulatory evaluation of the NDA. The study was conducted in 80 study centers worldwide and a total of 435 patients with advanced RCC were randomized (2:1) to receive pazopanib 800 mg once daily or placebo. The analysis of the

prespecified primary endpoint (progression-free survival) showed a large and significant improvement in PFS in patients treated with pazopanib compared to patients treated with placebo (HR 0.46, p<0.0000001), with a median PFS of 9.2 months in the pazopanib arm compared to a median of 4.2 months in the placebo arm. The safety profile revealed acceptable toxicities, which are generally similar to those known with the approved product sunitinib except for the higher incidences of hepatic dysfunction. Overall, the evidence, as presented by the sponsor, appears to support the proposed indication for pazopanib. The clinical review of submitted datasets and analyses is currently ongoing.

Protocol/Site Identification:

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Center # 34145: KORALEWSKI, Piotr NZOZ VESALIUS Practice ul. Smolensk 25a m 2, 31-108 Cracow, Poland	VEG105192	**19 patients received pazopanib, 8 patients received placebo**	treatment of patients with advanced renal cell carcinoma
Center # 24756: LEE, Eun-Sik Seoul National University Hospital, 28 Yongon-Dong, Chongno-Ku, Seoul 110744, Korea	VEG105192	**10 patients received pazopanib, 1 patient received placebo**	treatment of patients with advanced renal cell carcinoma

II. Site Selection/Rationale

The listed two sites essential for approval have been identified for inspection as per the clinical review team.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X___ Not applicable given that no patients from the United States or Canada were enrolled in the study.

___ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

__X__ There are no domestic data
__X__ Only foreign data are submitted to support the application. The key study was conducted in 23 countries. The largest enrollment (25%) was from Poland. The center selected for inspection as listed above had the largest enrollment (6.2%) in the study. It also had high incidences of hepatic dysfunction (6 of the 19 patients assigned to the pazopanib arm had Grade 2, 3, or 4 abnormalities in transaminases).
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): The Korean center selected for inspection had a higher response rate (50% in 10 patients that received pazopanib), with an estimated HR 0.234, which is lower than that (HR=0.46) of the overall population treated with pazopanib. In addition, 3 of the 10 patients had Grade 2 or 3 hepatic abnormalities in transaminases.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Should you require any additional information, please contact Kim Robertson (regulatory project manager) at 301-796-1441 or Y. Max Ning (medical reviewer) at 301-796-2321.

Concurrence: (as needed)

Y. Max Ning, M.D. _____ Medical Reviewer
V. Ellen Maher_____Medical Team Leader
Robert L. Justice, M.D._____ Division Director (for foreign inspection requests only)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
2/25/2009 06:33:38 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 17, 2009

TO: Kim Robertson, Regulatory Project Manager
Y. Max Ning, Medical Officer
Division of Oncology Drug Products

FROM: Robert Young
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-465

APPLICANT: GlaxoSmithKline
Philadelphia, PA

DRUG: Votrient (pazopanib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of patients with advanced renal cell carcinoma.

CONSULTATION REQUEST DATE: 02/18/2009

DIVISION ACTION GOAL DATE: 09/18/2009

PDUFA DATE: 10/19/2009

I. BACKGROUND:

Three clinical investigator inspections were conducted as part of the routine surveillance program in support of this application. The three sites were selected due to high enrollment.

The protocol inspected was: VEG105192 - A randomized, double-blind, placebo controlled, multi-center Phase III study to evaluate the efficacy and safety of pazopanib compared to placebo in patients with locally advanced and/or metastatic RCC (Renal Cell Carcinoma).

II. RESULTS (by Site):

Name and Location	# of Subjects:	Inspection Date	Final Classification
Piotr Koralewski Nzoz Vesalius Practice Ul Smolensk 25a m2 31-108 Krakow Poland	27	3 – 7 Aug 2009	Interim classification NAI
Janusz Rolski Institute Marie Skodowska-Curie Ul Garncarska 11 31-115 Krakow Poland	17	10 – 13 Aug 2009	Interim classification NAI
Ein-Sik Lee Seoul National University Hospital 28 Yongon-Dong Chongno-Ku Seoul 110744, Korea	11	6 – 10 July 2009	Interim classification VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **Piotr Koralewski**

Note: this report is based on participation in the inspection.

a. **What was inspected**: The administrative file, medication records, and consent forms for all subjects were inspected. Case histories for 16 of 27 enrolled

subjects were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**: The case histories were complete and in good order. No objectionable conditions were identified and no FDA Form 483 issued.

c. **Assessment of data integrity**: The data from this site is acceptable in support of the pending application.

2. **Janusz Rolski**

Note: this report is based on participation in the inspection.

c. **What was inspected**: The administrative file, medication records, consent forms and case histories for all 17 enrolled subjects were inspected. There were no limitations to the inspection.

d. **General observations/commentary**: The case histories were complete and in good order. A question was raised as to how progression of disease was to be determined and it was found after consultation with the sponsor that because the protocol was unclear the investigator had acted within the bounds of the protocol. No significant issues were identified.

c. **Assessment of data integrity**: The data from this site is acceptable in support of the pending application.

3. **Ein-Sik Lee**

a. **What was inspected**: The administrative file, medication records, consent forms and case histories for all 11 enrolled subjects were inspected. There were no limitations to the inspection.

b. **General observations/commentary**: In general, the case histories were complete and in good order. There were a few objectionable conditions which were described in a Form FDA 483 issued and to which the investigator has responded in writing:
   - ⇒ There was no source documentation that subjects had received a copy of their executed informed consent document, that Subject 601's ECOG evaluation was 0, and that Subjects 603, 786 and 790 had died. The investigator explained that he did not have subjects sign a consent received receipt, that the ECOG evaluation in question was done when the subject was not in clinic, but in the hospital and the evaluation result was directly entered into the CRF with a note; and that the site took the family's word that a subject had died. These are all acceptable procedures.
   - ⇒ Several CRF reportable entries were missed by the site, but found by the

monitor and duly reported: concomitant medications – 1% isoconazade, 1 liter 10% dextrose, and Medilac-DS; and a grade 1 hand-foot syndrome over several months in one subject.

c. **Assessment of data integrity**: Although there were a few lapses with data entry, these were caught and the data base properly updated. Although some regulatory violations were documented at this site, these are unlikely to impact data integrity, and the data from this site is acceptable in support of the pending application.

Observations noted above are based on preliminary communication with the field investigator; an inspection summary addendum will be submitted if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator and/or participation in the inspection; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT S K YOUNG
09/17/2009

TEJASHRI S PUROHIT-SHETH
09/17/2009

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 2, 2009
To:	Robert Justice, M.D. Division Director **Division of Drug Oncology Products (DDOP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Product Information Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, BSN, R.N. Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name(s):	VOTRIENT (pazopanib) Tablets
Application Type/Number:	NDA 22-465
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2009-311 2009-1070

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for VOTRIENT (pazopanib) Tablets. Please let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DDOP under separate cover.

2 MATERIAL REVIEWED

- Draft VOTRIENT (pazopanib) Tablets Prescribing Information (PI) submitted December 19, 2008 and revised by the Review Division throughout the current review cycle.
- Draft VOTRIENT (pazopanib) Tablets Medication Guide (MG) submitted on August 11, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

16 Pages Withheld as b(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAWNA L HUTCHINS
10/13/2009

CLAUDIA B KARWOSKI
10/13/2009
concur

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 8, 2009
To:	Robert Justice, MD, Director Division of Drug Oncology Products
Through:	Kristina Arnwine, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Lori Cantin, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Labels and Labeling Review (Second review)
Drug Name(s):	Votrient (Pazopanib) Tablets, 200 mg and 400 mg
Application Type/Number:	NDA 022465
Applicant:	GlaxoSmithKline
OSE RCM #:	2009-310

CONTENTS

1 INTRODUCTION 3
2 MATERIALS REVIEWED 3
3 RECOMMENDATIONS 3
3.1 Comments to the Division 3
3.2 Comments to the Applicant 4

1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products for a review of the revised Votrient labels in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant.

2 MATERIALS REVIEWED

The following revised container labels provided by the Applicant on June 10, 2009, were reviewed (see Appendix A for images):

- Container Label: 200 mg tablet, 30-count bottle
- Container Label: 200 mg tablet, 90-count bottle
- Container Label: 400 mg tablet, 30-count bottle
- Container Label: 400 mg tablet, 60-count bottle

Additionally, the revised package insert and medication guide (no images) submitted September 25, 2009, were reviewed.

We also evaluated DMEPA's recommendations pertaining to the original labels that were provided in OSE RCM# 2009-310 dated May 19, 2009.

3 RECOMMENDATIONS

Our evaluation determined that the Applicant has adequately responded to DMEPA's previous recommendations. However, upon our evaluation of the revised container labels submitted by the Applicant, we have one additional recommendation for the Applicant aimed at minimizing the potential for medication errors due to confusion between the two product strengths. Additionally, we provide two recommendations on the insert labeling in Section 3.1 *(Comments to the Division)* for discussion during the review team's label and labeling meetings. Section 3.2 *(Comments to the Applicant)* contains our recommendation for the container labels. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Sandra Griffith, OSE Regulatory Project manager, at 301-796-2445.

3.1 COMMENTS TO THE DIVISION

In order to ensure that practitioners are fully aware of the maximum dose of Votrient, we recommend relocating the statement "The dose of Votrient should not exceed 800 mg" from **Section 2.2 Dose Modification Guidelines** to **Section 2.1 Recommended Dosing**; or alternatively, the statement could be located in each section.

3.2 COMMENTS TO THE APPLICANT

Container Labels

We note the Applicant uses the color orange to represent 400 mg strength and the color green to represent the 200 mg strength. However, as presented, the Applicant uses a contrasting color "stripe" presented above the proprietary name (i.e. orange stripe on the 200 mg strength and green stripe on the 400 mg strength) which lessens the differentiation of the labels. Use the orange stripe on the 400 mg strength and the green stripe on the 200 mg strength.

2 Pages Withheld as b(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISTINA C ARNWINE on behalf of LORI G CANTIN
10/08/2009

KRISTINA C ARNWINE
10/08/2009

DENISE P TOYER
10/09/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Drug Oncology Products

Application Number: NDA 22-465

Name of Drug: VOTRIENT™ (pazopanib hydrochloride) Tablets; 200 mg, 400 mg

Applicant: GlaxoSmithKline

Material Reviewed:

Submission Date(s): December 18, 2008

Receipt Date(s): December 19, 2008

Submission Date of Structure Product Labeling (SPL): December 18, 2008

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the applicant's proposed labeling.

In this review the following issues/deficiencies have been identified:

1. In Highlights, the word VOTRIENT is in parentheses. Parentheses need to be removed.

2. Under the Dosage and Administration heading in Highlights, if there are multiple subheadings, each subheading must be preceded by a bullet point. Bullet points should be added for 2.1.

3. Subsection 12.2, Pharmacodynamics is listed in the FPI, but is not listed in the Table of Contents (TOC). It needs to be included in the TOC.

4. The same title for the boxed warning that appears in the Highlights must also appear at the beginning of the Table of Contents in uppercase letters and bold type.

5. The pregnancy category should appear under subsection 8.1 and not under Warning and Precautions.

6. In Section 11, Description, the sponsor should've included the route of administration (i.e. for oral use) See 21 CFR 201.57(c)(12)(B).

7. The sponsor included Section 12.2 in FPI; however it is missing in the TOC.

8. The sponsor should ensure that the Patient Counseling Information section contains all information (i.e., W&P, Adverse Reactions) for the prescriber to convey to the patient to use the drug safely and effectively. See 21 CFR 201.57(c)(18).

Recommendations

Given that labeling negotiations are still ongoing; these PLR comments will be conveyed to the applicant for correction of the issues. Similar comments were discovered during the SEALD Review of the label.

GlaxoSmithKline will address the identified deficiencies/issues and re-submit labeling. Labeling was reviewed on October 5, 2009.

_____
Kim J. Robertson
Consumer Safety Officer

Supervisory Comment/Concurrence:

_____
Frank Cross, Jr.
Chief, Project Management Staff

Drafted: KJR/October 6, 2009
Revised/Initialed: fhc/10- -09
Finalized: FCross/ 10- -09
Filename: C:\MY CSO\ROBERTSON\NDA's\22465 PAZOPANIB VOTRIENT\PM PLR Review
CSO LABELING REVIEW OF PLR FORMAT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIM J ROBERTSON
10/06/2009
PM PLR Labeling Review NDA 22-465; Votrient (pazopanib hydrochloride) Tablets 200 mg, 400 mg; RCC

FRANK H Cross
10/06/2009

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-465
APPLICANT	GLAXO WELLCOME MFG
DRUG NAME	VOTRIENT TABLETS
SUBMISSION DATE	December 19, 2008
SEALD REVIEW DATE	October 1, 2009
SEALD REVIEWER(S)	Abiola Olagundoye, PharmD
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

26 Pages Withheld as b(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABIOLA OLANGUNDOYE
10/02/2009

LAURIE B BURKE
10/02/2009