DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022465

NDA APPROVAL

GlaxoSmithKline
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology

Dear Ms. Cutler:

Please refer to your new drug application (NDA) dated December 18, 2008, received December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Votrient™ (pazopanib hydrochloride) tablets, 200 mg and 400 mg.

We acknowledge receipt of your submissions dated February 13 (3), 27, 2009; March 11, 31, 2009; April 1, 2, 3, 7, 9, 13, 27, and 30(3), 2009; May 1, 8, 13, 20, and 22, 2009; June 3, 8, 10, 18, and 25, 2009; July 17, 20, 28, and 31, 2009; August 3, 6, and 11, and 18, 2009; September 14, 16, 25(3), and 30, 2009; October 1, 2, 13, 14, 15(2), 16, and 19(2), 2009.

This new drug application provides for the use of Votrient™ (pazopanib hydrochloride) tablets, 200 mg and 400 mg, for the treatment of patients with advanced renal cell carcinoma.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease/condition does not exist in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of recurrence of hepatotoxicity from re-challenge, cardiotoxicity, and increased toxicity from hepatic impairment, and to assess a signal for a serious risk of Q-T prolongation and drug-drug interaction with Votrient™.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of recurrence of hepatotoxicity from re-challenge, cardiotoxicity, and increased toxicity in patients with hepatic impairment; and to assess a signal for a serious risk of Q-T prolongation and drug-drug interaction.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1549-1. Examine the safety of dose modification of pazopanib and patient rechallenge with pazopanib following hepatotoxicity. This examination should include at least 1,500 treated patients and may be derived from ongoing or completed trials, including VEG108844, VEG110727, and VEG110665.

The timetable you submitted on October 15, 2009, states that you will conduct this trial according to the following timetable:

Trial Completion Date: July 31, 2012
Final Report Submission: October 31, 2012

1549-2. Examine the cardiotoxicity, clinical cardiac events and changes in ejection fraction in your ongoing trial VEG108844.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol was submitted: May 29, 2008
Trial Completion Date: December 31, 2010
Final Report Submission: May 31, 2011

1549-3. Submit the final report of the hepatic impairment trial, protocol NCI 8063.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol was submitted:	October 19, 2007
Trial Completion Date:	January 15, 2010
Final Report Submission:	May 15, 2010

1549-4. Submit the final report of the dedicated QTc prolongation trial, VEG111485.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol was submitted:	January 27, 2009
Trial Completion Date:	February 27, 2010
Final Report Submission:	July 30, 2010

1549-5. To adequately determine the influence of strong CYP3A4 inhibitors on the exposure of pazopanib following oral clinical pazopanib doses, conduct a drug-drug interaction trial in patients using clinical doses of oral pazopanib and a strong CYP3A4 inhibitor (e.g., ketocoanzole). The protocol should be submitted prior to initiation for review and concurrence.

The timetable you submitted on October 15, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	January 15, 2010
Trial Completion Date:	October 31, 2010
Final Report Submission:	February 28, 2011

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIRMENTS OF SECTION 506B

We remind you of your postmarketing commitments in your submissions dated October 14 and 15, 2009. These commitments are listed below.

1549-6. Submit the final analysis of overall survival in your ongoing trial VEG105192.

The timetable you submitted on October 14, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol was submitted:	February 3, 2006
Trial Completion Date:	January 31, 2010
Final Report Submission:	May 31, 2010

1549-7. Pending the outcome of trials VEG 108844, 110727, or NCI 8063, you may need to develop a 100 mg dosage form (tablet) to allow for proper dose reductions of Votrient™ (Pazopanib) when liver enzyme elevations occur. The 100 mg dosage form should be sufficiently distinguishable from the 200 mg and 400 mg tablets. (b) (4)

The timetable you submitted on October 15, 2009, states that you will conduct this commitment according to the following timetable:

Final Protocol Submission:	September 30, 2010
Final Report Submission:	December 31, 2001

1549-8. Submit the final report with complete datasets for ongoing trial VEG108844 titled: A Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma".

The timetable you submitted on October 15, 2009, states that you will conduct this study according to the following timetable:

Final Protocol was submitted:	May 29, 2008
Trial Completion Date:	December 31, 2010
Final Report Submission:	May 31, 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (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)).

Your proposed REMS, submitted on October 15, 2009, amended on October 15 and 19, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

Your assessment of the REMS should include:

a. An evaluation of patients' understanding of the serious risks of Votrient™ (pazopanib hydrochloride).
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022465
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022465
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 022465
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert, and Medication Guide dated October 16, 2009 Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022465.**"

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission

"**Final Printed Carton and Container Labels for approved NDA 022465**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure
Labeling and Medication Guide
REMS

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

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

/s/

RICHARD PAZDUR
10/19/2009