

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-465

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-465

SUPPL #

HFD # 150

Trade Name Votrient Tablets; 200 mg and 400 mg

Generic Name (pazopanib hydrochloride)

Applicant Name GlaxoSmithKline

Approval Date, If Known October 19, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kim J. Robertson
Title: Consumer Safety Officer
Date: October 2, 2009

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

10/02/2009

Exclusivity Summary for Votrient 2009; NME NDA 22-465

ROBERT L JUSTICE

10/06/2009

CONFIDENTIAL

m1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 22-465).


Craig Wozniak

November 2008

ACTION PACKAGE CHECKLIST

NDA # 22-465	NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Votrient™ 200 mg; 400 mg Established Name: (pazopanib) Dosage Form: Tablets		Applicant: GlaxoSmithKline
RPM: Kim J. Robertson		Division: HFD-150 Phone # (301) 796-1441
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date: ❖ Action Goal Date (if different)		October 19, 2009 October 19, 2009
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ Advertising <i>(approvals only)</i> Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed <i>(indicate dates of reviews)</i>		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1S	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p>
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Division Director: October 19, 2009 ; Office Director: October 19, 2009
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	October 15, 2009
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	December 19, 2008
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	October 7, 2009
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	August 11, 2009
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	October 13, 2009

❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> X DDMAC 10/02/09 X SEALD 10/01/09 X Other reviews DMEPA:10/13/09 DEPI:TBD Pending <input type="checkbox"/> Memos of Mtgs
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	September 28, 2009
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	Included Pending Signature
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input type="checkbox"/> None October 15, 2009 October 14 and 15, 2009
Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Please refer to Outgoing Communications Tab
❖ Internal memoranda, telecons, email, etc.	October 19, 2009
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs)—Ofc. Of Surveillance and Epidemiology 	N/A <input type="checkbox"/> No mtg June 16, 2008 (CMC PreNDA) July 15, 2008 No mtg December 7, 2006, August 14, 2007, December 18, 2007, May 1, 2008 Type C; QbD Meeting Minutes- November 3, 2008
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	October 5, 2009 October 6, 2009
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	October 2, 2009
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	Primary Review: October 7, 2009; CMC Memo: October 20, 2009 Branch Chief Review: October 13, 2009 CMC Division Director Review: October 8, 2009
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X Biometrics Review September 30, 2009
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No

❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	October 7, 2009 (See page 243 of CMC Review)
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	N/A <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: October 9, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	
• Facility review (<i>indicate date(s)</i>)	<input type="checkbox"/> Requested
• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)	<input type="checkbox"/> Accepted
	<input type="checkbox"/> Hold
❖ NDAs: Methods Validation N/A	<input type="checkbox"/> Completed
	<input type="checkbox"/> Requested
	<input type="checkbox"/> Not yet requested
	<input type="checkbox"/> Not needed
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	September 18, 2009, TL Review, September 18, 2009; Associate Director P/T Review: October 9, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

· Clinical review(s) <i>(indicate date for each review)</i>	Med. Offc. Review: October 15, 2009 ; CDTL Review: October 13, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 19 of Clinical Review
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	None DEPI-TBD
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	X Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	Page 50 of Clinical Review
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	DRISK Review of REMS- October 16, 2009
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	X Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	September 17, 2009
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> September 15, 2009; Stat Team Leader September 16, 2009
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 21, 2009

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.



NDA 22-465

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

GlaxoSmithKline
ATTENTION: Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
PO Box 5089
Collegeville, Pennsylvania 19428-0989

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated December 18, 2008, receipt date December 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pazopanib hydrochloride tablets, 200 mg and 400 mg.

We also refer to your February 13, 2009, correspondence, received February 13, 2009, requesting review of your proposed proprietary name, Votrient. We have completed our review of the proposed proprietary name, Votrient, and have concluded that it is acceptable.

The proposed proprietary name, Votrient, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your February 13, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

**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
5/7/2009 07:39:23 PM

Robertson, Kim

From: Cantin, Lori
Date: Tuesday, April 28, 2009 11:10 AM
To: Robertson, Kim
Cc: Toyer, Denise P; Holquist, Carol A; Arnwine, Kristina; Griffith, Sandra J; Campbell, Cheryl
Subject: NDA 22-465: 45 day email: Proprietary Name Review: Votrient

Importance: High

Attachments: Tables for 45 day email.doc; Picture (Enhanced Metafile)

Hello Kim:

This email is to notify you that the Division of Medication Error Prevention and Analysis (DMEPA) has completed our preliminary review of the proposed name, Votrient. .

In our review of the proposed name, Votrient, we did identify one name, (b) (4), that has orthographic and phonetic similarity to, and overlapping product characteristics with, (b) (4)
(b) (4)

Please share this email and the attached information with your team. We would be happy to meet with the Division to discuss our analysis, if needed. Otherwise please let us know if you concur or do not concur with our assessment and provide your response along with any additional comments on the proposed proprietary name, Votrient, by Friday, May 1, 2009.



Tables for 45
day email.doc (1..

(b) (4)

As part of our name risk assessment, we considered all of the orthographic and phonetic characteristics of the names, and the product characteristics of the proposed products, Votrient and (b) (4)

Orthographically, Votrient looks like (b) (4)

(b) (4)

(b) (4)

Thanks,
Lori

Lori Cantin, R.Ph.
CDR, U.S. Public Health Service
Safety Evaluator
FDA/CDER/OSE/DMEPA
White Oak Campus, Bldg. 22
7903 New Hampshire Ave
Silver Spring, MD 20993-0002
☎ (301) 796-1212 (Office)
☏ (301) 796-9865 (Fax)
✉ lori.cantin@fda.hhs.gov

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **22-465** Supplement # **N/A** Efficacy Supplement Type **SE-** **N/A**

Proprietary Name: **VOTRIENT® Tablets**
Established Name: **(pazopanib)**
Strengths: **200 mg and 400 mg**

Applicant: **GlaxoSmithKline**
Agent for Applicant (if applicable): **N/A**

Date of Application: **December 19, 2008**

Date of Receipt: **December 19, 2008**

Date clock started after UN: **N/A**

Date of Filing Meeting: **February 3, 2009**

Filing Date: **February 2, 2009**

Action Goal Date (optional): **September 14, 2009**

User Fee Goal Date: **October 19, 2009**

Indication(s) requested: **Votrient is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).**

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES NO
2. This application is an eNDA or combined paper + eNDA YES X
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance? YES NO
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments: N/A

3. This application is an eCTD NDA. YES NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, X- Years NO
5yrs

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 65, 747

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) August 14, 2007; April 8, 2008 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) September 17, 2007; June 16, 2008 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES X NO
- Risk Management Plan consulted to OSE/IO? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 3, 2009

NDA #: 22-465

DRUG NAMES: **VOTRIENT® (pazopanib) Tablets**, 200 mg and 400 mg

APPLICANT: GlaxoSmithKline

BACKGROUND: GlaxoSmithKline has submitted an NDA for VOTRIENT®; an oral angiogenesis inhibitor professing to target VEGFR-1, -2, -3, PDGFR- α and β , and c-Kit. Pazopanib is being evaluated in clinical development for the treatment of a variety of tumors.

ATTENDEES: Assigned Reviewers

ASSIGNED REVIEWERS (including those not present at filing meeting): See Below↓

Discipline/Organization

Reviewer

Medical:	Yang (Max) Ning, M.D.
Secondary Medical:	V. Ellen Maher, M.D.
Statistical:	Yu-Ling Chang, Ph.D., Shenghui Tang, Ph.D.
Pharmacology:	Robeena Aziz, Ph.D and Whitney Helms, Ph.D., Leigh Verbois, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Sharmista Chatterjee, Ph.D., Brian D. Rogers, Ph.D., T. Ocheltree, Ph.D
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Bahru Habtemariam, Julie Bullock, Pharm.D., Ph.D., Brian Booth, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Robert S.K. Young, M.D.
OPS:	N/A
Regulatory Project Management:	Kim J. Robertson, CSO
Other Consults:	DMETS, SEALD, DDMAC, DSI, OSE, DEPI, QT/IRT, DMEPA

Per reviewers, are all parts in English or English translation? YES NO
If no, explain: N/A

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:

• Advisory Committee Meeting needed? YES, date if known October 5, 2009 NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	<input checked="" type="checkbox"/>	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>

• Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
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• GLP audit needed? YES NO

CHEMISTRY			FILE	<input checked="" type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
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• Establishment(s) ready for inspection? YES NO
 • Sterile product? YES NO
 If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
Any comments: N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Kim J. Robertson
Consumer Safety Officer

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

09/25/2009

NDA Regulatory Filing Review for VOTRIENT (pazopanib) Tablets; 200 mg and 400 mg; 22-465

FRANK H Cross

09/28/2009

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The applicant has a large number of ongoing and previous trials with this drug that have used the recommended dose modification schema. The applicant will pool this data and examine the safety of re-challenging patients with pazopanib.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The applicant has a large number of ongoing and previous trials with this drug that have used the recommended dose modification schema. The applicant will pool this data and examine the safety of re-challenging patients with pazopanib.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs?
 - Are the objectives clear from the description of the PMR?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

PMR Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products
Indication: For the treatment of advanced renal cell carcinoma

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

PMR Schedule Milestones: Final protocol Submission Date: 5/29/2008
Study/Clinical trial Completion Date: 12/31/2010
Final Report Submission Date: 5/31/2011
Other: Labeling changes, if needed NA

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To assess cardiotoxicity from the use of pazopanib

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial ongoing (VEG108844)

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
to examine cardiotoxicity

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

PMR Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products

PMR 1549-3 . Submit the final report of the hepatic impairment clinical trial NCI 8063.
Description:

PMR/PMC Schedule Milestones: Final protocol Submission Date: 10/19/2007
Study/Clinical trial Completion Date: 01/15/2010
Final Report Submission Date: 05/15/2010

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A hepatic impairment trial is ongoing. Interim data are available in patients with normal hepatic function and in patients with mild and moderate hepatic impairment. As 6/5/2009 42 patients have been enrolled in study NCI 8063, but no patient with severe hepatic impairment has been enrolled.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Due to findings that pazopanib metabolim takes place in the liver a dedicated PK trial in patients with mild, moderate and severe hepatic impairment is needed in order to identify safe doses for patients with hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Study NCI 8063 is a phase 1 trial designed to establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of pazopanib in patients with varying degrees of hepatic impairment (mild, moderate, and severe). The starting doses were 800, 400, 200, and 100 mg once daily for patients with normal hepatic function and patients with mild, moderate, and severe hepatic impairment, respectively.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products.

PMR 1549-4 Description: Submit the report of the dedicated QTc prolongation clinical trial VEG111485.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/27/2009
Study/Clinical trial Completion Date: 02/27/2010
Final Report Submission Date: 07/30/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

QT data are available from previous phase 1 and phase 2 clinical trials. However, due to suboptimal study designs, findings of the previous trials are deemed inconclusive. The sponsor has initiated a phase 1 clinical trial with optimal study design to determine the influence of pazopanib on QT intervals.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In the randomized phase 3 trial 1% of pazopanib treated subjects had QTc elevations of > 500 msec. However, the phase 1 dose escalation trial found no dose-QTc or concentration-QTc relationship. The proposed QT study is planned to determine whether pazopanib has potential for QTc prolongation.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a phase 1, randomized, double-blind, placebo-controlled, parallel group study designed to estimate the effects of repeated, once daily oral dosing of pazopanib on cardiac repolarization (QTc interval duration) as compared with placebo in subjects with solid tumors. Moxifloxacin, a drug known to cause mild QTc interval prolongation, is included as a positive control to validate the ability of the study to detect a small prolongation in the QTc interval. Digital 12-lead electrocardiograms (ECGs) will be extracted from continuous ECG recordings obtained via a Holter monitor. The effects of pazopanib and moxifloxacin on cardiac repolarization will be compared with placebo. This study will also assess the pharmacokinetic-pharmacodynamic relationship between plasma concentrations of pazopanib and its metabolites and their effects, if any, on cardiac repolarization, specifically on the QT interval.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
QT prolongation assessment using non-thorough QT trial design.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

PMR Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products
Indication: For the treatment of advanced renal cell carcinoma

PMR 1549-5 Description: 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. ketoconazole). The protocol should be submitted prior to initiation for review and concurrence.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/15/2010
Study/Clinical trial Completion Date: 10/31/2010
Final Report Submission Date: 02/28/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

PK evaluation during NDA review indicated the need for an *in vivo* trial. PK trials submitted with the NDA used either non-clinical pazopanib dose (0.4 mg) or weak CYP3A4 inhibitor (lapatinib), which indicated drug interaction. Therefore additional trial is needed to accurately determine the magnitude of pazopanib exposure changes when clinical doses of pazopanib are concomitantly used with strong CYP3A4 inhibitors.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The proposed trial will used a clinical dose of 1 oral pazopanib along with a known strong CYP3A4 inhibitor. The drug-drug interactions like this can lead to increased risk of toxicity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A drug-drug interaction clinical trial is needed to adequately determine the influence of strong CYP3A4 inhibitors on the exposure of pazopanib following clinical oral doses of pazopanib. To be acceptable the study should use oral formulation pazopanib at the clinical dose level (400 to 800 mg) along with a strong CYP3A4 inhibitor (e.g. Ketoconazole) at the appropriate clinical dose. The protocol should be submitted prior to initiation for review and concurrence.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An ongoing trial in patients with metastatic or locally advanced renal cell carcinoma.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
An analysis of overall survival from an ongoing trial in patients with metastatic or locally advanced renal cell carcinoma. At NDA submission, the applicant provided data from this trial concerning progression-free survival.

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

PMC Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products

PMC 1549-7
Description:

Pending the outcome of studies 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)

PMR/PMC Schedule Milestones: Final protocol Submission Date: 09/30/2010
Final Report Submission Date: 12/31/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Pending the outcome of studies VEG 108844, 110727, or NCI 8063, a lower strength tablet, 100 mg, may be needed for dose reductions to address liver enzyme elevations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See above for review issue. To address liver enzyme elevations, the sponsor proposed initial dose reduction to 600 mg, and in steps of 200 mg for subsequent reductions. However, to achieve a meaningful exposure reduction, an initial dose reduction should be to 400 mg, and subsequent dose adjustment should be in steps of 100 mg. Because pazopanib is currently available only as a 200 and 400 mg tablet formulation, a new 100 mg tablet formulation is needed to implement the recommended dose modification scheme.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical study may not be required to fulfill the proposed post marketing commitment. The sponsor should first conduct the appropriate *in vitro* dissolution studies to compare dissolution and quality profiles of the 100 mg versus the 200 mg and 400 mg tablets. If the profiles are dissimilar, an *in vivo* study may be needed.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

PMC Development Template

NDA: 022465
Drug: Votrient™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg
Sponsor: GlaxoSmithKline
Division: Division of Drug Oncology Products
Indication: For the treatment of advanced renal cell carcinoma

PMC 1549-8
Description: 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".

PMR/PMC Schedule Milestones: Final protocol Submission Date: 5/29/2008
Study/Clinical trial Completion Date: 12/31/2010
Final Report Submission Date: 5/31/2011
Other: NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This study compares the safety and efficacy of pazopanib to the most widely used drug for the treatment of advanced renal cell carcinoma, sunitinib.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Assess the relative safety and efficacy of pazopanib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Ongoing clinical trial in patients with metastatic or locally advanced renal cell carcinoma comparing pazopanib and sunitinib.
--

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)
Examination of the safety and efficacy of pazopanib.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for NDAs)

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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/s/

KIM J ROBERTSON

10/16/2009

PMRs/PMCs for Votrient; NDA 22-465

AMNA IBRAHIM

10/22/2009

**Post Marketing Requirements
(PMRs)
For
VOTRIENT™ (pazopanib hydrochloride) Tablets 200 mg, 400 mg**

- 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., ketoconazole). 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

From: ellen.s.cutler@gsk.com
Sent: Thursday, October 15, 2009 1:09 PM
To: Robertson, Kim
Subject: Re: NDA 022465 Votrient PMR/PMC

Attachments: PMR PMC response 2.doc

Hello Kim,
Here's the completed PMR/PMC document. I will have it sent through the gateway this afternoon.

I will be sending the REMS doc shortly and a response to your 10/13 request for the list of studies using the new Guidelines for Management of Treatment Emergent Hepatotoxicity.

Please don't hesitate to call if anything further is needed.
Kind regards,
Ellen

Ellen Cutler
GlaxoSmithKline
Regulatory Affairs
)-917-6823

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"Robertson, Kim" <Kim.Robertson@fda.hhs.gov>

To ellen.s.cutler@gsk.com

cc

14-Oct-2009 18:58

Subject

Ellen:

GSK will need to submit to us by COB **tomorrow, Thursday, October 15, 2009** their responses with regard to the PMRs/PMCs. An earlier response than COB is also

appreciated, but we must have them tomorrow. Please see the attached Word .doc:

'OTRIENT PMR PMC response.10.14.2009.doc>>

Kim J. Robertson

Consumer Safety Officer

Division of Drug Oncology Products

Phone: (301) 796-1441

*Fax: (301) 796-9845[attachment "VOTRIENT PMR PMC response.10.14.2009.doc"
deleted by Ellen S Cutler/ PharmRD/ GSK]*

NDA 022465 Votrient™ (pazopanib) Tablets

Post-marketing Requirements (PMRs):

1549-1. Description of Requirement: 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(s) including VEG108844, VEG110727, and VEG110665.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Final Protocol Submission:

Trial Completion Date: 07/31/2012

Final Report Submission: 10/31/2012

1549-6. Description of Requirement: 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. ketoconazole). The protocol should be submitted prior to initiation for review and concurrence.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Final Protocol Submission: January 15, 2010

Trial Completion Date: 10/31/2010

Final Report Submission: 02/28/2011

Post-marketing Commitment (PMC):

We remind you of your postmarketing study commitment in your submission dated DATE. This commitment is listed below.

1549-7. Description of Commitment: Pending the outcome of studies 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 <<insert date>> states that you will conduct these studies according to the following timetable:

Final Protocol Submission: 09/30/2010

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Final Report Submission: 12/31/2011

1549-8 Description of Commitment: 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 <<insert date>> states that you will conduct these studies according to the following timetable:

Final Protocol Submission: 05/29/2008

Trial Completion Date: 12/31/2010

Final Report Submission: 05/31/2011

CONFIDENTIAL

Appendix A

PMR 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(s).

GSK proposes to analyze pooled data from pazopanib treated subjects from the following sources:

Source / Population	Number of Subjects	Protocol Submission Date MM/DD/YYYY	Trial Completion Date MM/DD/YYYY	Final Report Submission MM/DD/YYYY
(b) (4)				
VEG108844 Phase III RCC	438*	05/29/2008	12/31/2010*	05/31/2011*
(b) (4)				
VEG110727 Phase III Sarcoma	240*	07/31/2008	12/31/2010*	05/31/2011*
VEG110665 Phase III Ovarian	450*	02/09/2009	1/31/2012*	07/31/2012*
	Total: 1796*			

* anticipated

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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/s/

KIM J ROBERTSON

10/15/2009

October 15 GSK Response to FDA October 14 Response

From: Robertson, Kim
Sent: Tuesday, October 13, 2009 6:10 PM
To: 'ellen.s.cutler@gsk.com'
Subject: NDA 22-465 PMR Comment

Importance: High
Ellen:

Please see the information request stemming from the PMRs/PMC submitted to GSK:

- Please provide a list of pazopanib clinical studies (ongoing or to be conducted) that have used the new Guidelines for Management of Treatment Emergent Hepatotoxicity since May 2007. Please specify the size of the studies in the list.

Another comment, as it pertains to the PMRs is forthcoming Ellen.

Thank you,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

CONFIDENTIAL

FDA request:

Please provide a list of pazopanib clinical studies (ongoing or to be conducted) that have used the new Guidelines for Management of Treatment Emergent Hepatotoxicity since May 2007. Please specify the size of the studies in the list.

Note: This list only includes pazopanib monotherapy studies. Studies of pazopanib in combination with other agents are not included.

Study ID	Brief Description	Start Date	Actual or Projected Completion Date	Target Enrollment (N)
Ongoing or Completed Studies				
VEG10004	Phase I Radiolabel Study	7/18/2007	7/1/2008	10
VEG109693	Japanese Phase 1 Monotherapy in Solid Tumors	9/10/2007	7/31/2010	6
VEG108838	Phase 3 Pazopanib +/- Lapatinib in IBC	12/4/2007	6/29/2012	60
VEG109609	Phase 2 Pazopanib in NSCLC	2/7/2008	4/20/2009	14
VEG108844	Phase 3 Pazopanib versus Sunitinib in RCC	8/14/2008	11/12/2010	438 (876 total subjects; 1:1 randomization)
VEG110727	Phase 3 Pazopanib Sarcoma	10/9/2008	6/15/2012	240 (360 total subjects; 2:1 randomization)
(b) (4)				
VEG111485	Phase 1 QTc Study in Solid Tumors	3/19/2009	2/26/2010	60
VEG110655	Phase 3 Ovarian Maintenance	5/26/2009	12/31/2014	450 (900 total subjects; 1:1 randomization)
Studies Starting in 2010				
(b) (4)				



(b) (4)

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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/s/

KIM J ROBERTSON

10/15/2009

October 13 PMR FDA Comment stemming from PMRs/PMCs sent to GSK

From: Robertson, Kim
Sent: Friday, October 09, 2009 4:54 PM
To: 'ellen.s.cutler@gsk.com'
Subject: NDA 22-465 Votrient Deliverables

Importance: High

Attachments: VOTRIENT Label Oct 9 Labeling Post Meeting.doc
Hello Ellen:

Please see the following items we assured GSK we would be sending:

October 9 Draft Labeling with FDA Comments:



VOTRIENT
| Oct 9 Labelir

DMEPA Comments to GSK with regard to the Carton and Container:

- 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.

Draft PMRs/PMC (*Note-provide dates by COB Monday, October 12, 2009):

PMRs:

- 1549-1. Description of Requirement:** 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(s).

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: MM/DD/YYYY
Trial Completion Date: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

- 1549-2. Description of Requirement:** Examine the cardiotoxicity, clinical cardiac events and changes in ejection fraction, in your ongoing trial VEG108844. Provide complete datasets with the final report.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: MM/DD/YYYY
Trial Completion Date: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

- 1549-3. Description of Requirement:** Submit the final analysis of overall survival in your ongoing trial VEG105192. Provide complete datasets with the final report.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: MM/DD/YYYY
Trial Completion Date: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

- 1549-4. Description of Requirement:** Submit the final report of the hepatic impairment clinical trial of protocol NCI 8063.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: October 19, 2007
Trial Completion Date: MM/DD/YYYY
Final Report Submission: May XX 2010

- 1549-5. Description of Requirement:** Submit the report of the dedicated QTc prolongation clinical trial VEG111485.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: April 7, 2008
Trial Completion Date: MM/DD/YYYY
Final Report Submission: March XX 2010

- 1549-6. Description of Requirement:** 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. ketoconazole). The protocol should be submitted prior to initiation for review and concurrence.

The timetable you submitted on <<insert date>> states that you will conduct this trial according to the following timetable:

Protocol Submission: January 15, 2010
Trial Completion Date: MM/DD/YYYY
Final Report Submission: May XX, 2010

PMC:

We remind you of your postmarketing study commitment in your submission dated DATE. This commitment is listed below.

1549-7. Description of Commitment: 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 <<insert date>> states that you will conduct this study according to the following timetable:

Protocol Submission: December 4, 2009
Final Report Submission: August 4, 2010

***Note: Submit the labeling back to us by Monday, October 12, 2009.**
We need GSK's edits right away for a subsequent labeling meeting.

Regards,
Kim

*Kim J. Robertson
Consumer Safety Officer
Division of Drug Oncology Products
Phone: (301) 796-1441
Fax: (301) 796-9845*

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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/s/

KIM J ROBERTSON

10/15/2009

October 9 Votrient Deliverables to GSK; Initial FDA PMCs/PMRs to GSK

Jenney, Susan

From: Jenney, Susan
Sent: Monday, October 19, 2009 10:22 AM
To: 'ellen.s.cutler@gsk.com'; Robertson, Kim
Subject: RE: NDA 22-465 DRISK Review of REMS
Attachments: Template A Proposed REMS Oct 16 .doc

Good morning Ellen:

Thank you for your reply sent yesterday for Votrient. After our review, Template A has been revised (see attached file). Please let us know your response as soon as possible. Also, send in your response through official channels.

Contact me or Kim if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan

Susan Jenney, MS
Regulatory Project Manager for Safety (Acting)
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

From: ellen.s.cutler@gsk.com [mailto:ellen.s.cutler@gsk.com]
Sent: Sunday, October 18, 2009 11:03 PM
To: Robertson, Kim; Jenney, Susan
Subject: Re: NDA 22-465 DRISK Review of REMS

Hello Kim and Susan,
Please find attached the revised Appendix B incorporating the revisions from DRISK. (Template A is attached below.)

Please let me know if anything further is needed.
Kind regards,
Ellen

Ellen S Cutler/PharmRD

16-Oct-2009 17:46

USRA Mail code: UP4110 (office 4-1240) 8-282-6823; 1-610-917-6823
To "Robertson, Kim" <Kim.Robertson@fda.hhs.gov>
cc
Subject Re: NDA 22-465 DRISK Review of REMS [Link](#)

10/19/2009

Hi Kim,

Please find attached the revised Appendix A incorporating the revisions from DRISK with a GSK revision in section IIA.

As mentioned, I will provide a revised Appendix B on Monday morning when I have the appropriate sign off. We are in agreement with inclusion of 4 Medication Guides with each 120 count bottle of Votrient however I need to obtain approval from our packaging team before committing. We are in agreement with conducting the required assessments, but again, I need to obtain the appropriate approvals.

I will work with you on Monday to expedite any needed documents in an effort to obtain a timely action.

Have a great weekend.

Kind regards,

Ellen

Ellen Cutler
GlaxoSmithKline
Regulatory Affairs
610-917-6823

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"Robertson, Kim" <Kim.Robertson@fda.hhs.gov>

16-Oct-2009 16:42

To ellen.s.cutler@gsk.com

cc susan.p.spooner@gsk.com

Subject NDA 22-465 DRISK Review of REMS

Hello Ellen:

Please see the Word document that contains comments from our DRISK group with regard to your REMS:

<<Votrient REMS Review DRISK 10-16-09 FINAL.doc>>

We need GSK to provide a revised REMS by 5:30PM today. If GSK is able to provide the revised REMS sooner, that would be greatly appreciated.

Regards,

im

Kim J. Robertson

10/19/2009

Consumer Safety Officer

Division of Drug Oncology Products

Phone: (301) 796-1441

Fax: (301) 796-9845[attachment "Votrient REMS Review DRISK 10-16-09 FINAL.doc" deleted by Ellen S Cutler/PharmRD/GSK]

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

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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/s/

SUSAN JENNEY
10/19/2009

Jenney, Susan

From: Jenney, Susan
Sent: Wednesday, October 14, 2009 10:31 AM
To: 'ellen.s.cutler@gsk.com'
Cc: Robertson, Kim
Subject: REMS Template and Supporting Document

Attachments: REMS Template A B (Revised 5.18.09).doc

Good morning Ms. Cutler:

In order to complete the REMS submission for Votrient, please submit the attached REMS template with sections completed for Medication Guide and Timetable for Submission of Assessments. Submit your document through official channels and send a courtesy copy by e-mail as soon as possible.

Contact Kim Robertson or me if you have any comments or questions. Please confirm you have received this e-mail.

Thank you,
Susan



REMS Template
A B (Revised 5.1..

Susan Jenney, MS
Regulatory Project Manager for Safety (Acting)
Division of Drug Oncology Products
Office of Oncology Drug Products
OND/CDER/FDA
301-796-0062
301-796-9845 (FAX)
Susan.Jenney@fda.hhs.gov

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22465

ORIG-1

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VOTRIENT TABLETS

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/s/

SUSAN JENNEY
10/14/2009



NDA 022465

INFORMATION REQUEST

GlaxoSmithKline
Attention: Ellen S. Cutler, Senior Director, US Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Votrient™ (pazopanib) Tablets.

We also refer to your August 11, 2009, submission, containing your proposed Medication Guide.

We are reviewing the Medication Guide section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

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)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Votrient™ (pazopanib) to ensure that the benefits of the drug outweigh the risk of death related to hepatotoxicity.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Votrient™ (pazopanib) 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). FDA has determined that Votrient™ (pazopanib) 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).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Votrient™ (pazopanib).

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include:

- a. An evaluation of the patients’ understanding of the serious risks of Votrient™ (pazopanib).
- 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

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22465
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 22465
PROPOSED REMS-AMENDMENT**

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

If you have any questions, call Susan Jenney, Acting Regulatory Project Manager for Safety, at (301) 301-796-0062 or Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center of Drug Evaluation and Research

Appendix A: Medication Guide REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B:

**REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Medication Guide
 - b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

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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/s/

AMNA IBRAHIM
10/15/2009
For Dr. Robert Justice

From: Mesmer, Deborah
Sent: Thursday, September 24, 2009 1:17 PM
To: 'susan.p.spooner@gsk.com'
Cc: 'ellen.s.cutler@gsk.com'
Subject: NDA 22-465: revised CMC comment

From: Deborah Mesmer, Regulatory Health Project Manager, ONDQA

To: Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs, GSK
Cc: Ellen S. Cutler, Senior Director, US Regulatory Affairs, GSK

Please refer to your NDA 22-465 VOTRIENT™ (pazopanib hydrochloride) Tablet, 200mg; 400 mg.

We also refer to GlaxoSmithKline's submission dated September 14, 2009, and to the communication from FDA sent by email to Ms. Ellen Cutler and Dr. Susan Spooner on September 22, 2009, regarding the Chemistry, Manufacturing, and Controls sections of your submission. The following revised comment will supersede that conveyed by FDA on September 22, 2009.

Your data do not support your proposed X_{90} acceptance criterion for the (b) (4) drug substance. The Lot numbers 061130243, 061130242, 061130015, 061130241, 061130240, 061130239, and 061130457 do not appear in your cross-reference Table 2 contained in your response to Deficiency 1b of our September 4, 2009, communication. Therefore, adopt the supported acceptance criterion of *Not greater than* (b) (4) for X_{90} .

We request your response by Friday, September 25, 2009, so we may continue our review of your application.

FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science

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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/s/

DEBORAH M MESMER
09/25/2009

From: Mesmer, Deborah
Sent: Tuesday, September 22, 2009 4:07 PM
To: susan.p.spooner@gsk.com
Cc: 'ellen.s.cutler@gsk.com'
Subject: RE: NDA 22-465 pazopanib CMC comment

From: Deborah Mesmer, Regulatory Health Project Manager, ONDQA

To: Ellen S. Cutler, Senior Director, US Regulatory Affairs, GSK
Cc: Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs, GSK

Please refer to your NDA 22-465 VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg. We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request your response by Friday, September 25, 2009, so we may continue our review of your application.

Your data do not support your proposed X₉₀ acceptance criterion for the (b) (4) drug substance. The Lot numbers 061130243, 061130242, 061130015, 061130241, 061130240, 061130239, and 061130457 do not appear in your cross-reference Table 2 contained in your response to Deficiency 1b of our September 4, 2009, communication. Therefore, adopt the supported acceptance criterion of *Not* (b) (4) for X₉₀.

FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science
301-796-4023
deborah.mesmer@fda.hhs.gov

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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/s/

DEBORAH M MESMER
09/23/2009

From: Mesmer, Deborah
Sent: Thursday, September 10, 2009 5:09 PM
To: 'susan.p.spooner@gsk.com'
Subject: FDA Comments for NDA 22-465 TCON on September 14, 2009

Dear Dr. Spooner,

Thank you for the teleconference dial-in number. Please note the correspondence below.

From: Deborah Mesmer, Regulatory Health Project Manager, ONDQA

To: Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs, GSK

Please refer to your NDA 22- 465 VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg. We have the following comments for discussion at the teleconference meeting scheduled for Monday, September 14, 2009:

- 1) There is excessive variability in dissolution performance for the 91 lots of drug product data provided. Of these 91 lots, 17 % failed a pair wise comparison of dissolution profiles using the f2 metric. This suggests a failure of bioequivalence between lots. Tighten your dissolution specification so as to be commensurate with a level of quality which is less likely to release batches which are potentially bio-inequivalent (e.g., Q (b) at 30 minutes). Alternatively and at your discretion, you may perform a bioequivalence study with batches at the highest and lowest extremes of dissolution performance to support that your currently proposed specification will not release drug product batches which are bio-inequivalent.

(b) (4)

- 3) There is better agreement between observed versus predicted using the mixed effect model when the predicted is greater than (b) dissolved. As you reevaluate the design space, we recommend that you use dissolution criteria that include a predicted value of at least (b) dissolved.

- 4) We note that all two-way interactions, three-way interactions, and the quadratic terms are all statistically significant in determining the amount dissolved. Therefore, it is impossible to establish the design space as a simple rectangle in this case. (b) (4)

(b) (4)

From: susan.p.spooner@gsk.com [mailto:susan.p.spooner@gsk.com]
Sent: Thursday, September 10, 2009 4:57 PM
To: Mesmer, Deborah
Subject: RE: NDA 22-465 GSK Dial-in Details and E-mail Authorization

Dear Debbie,

Please find below the GSK dial-in conference details for the teleconference between GSK and FDA schedule for September 14, 2009 from 3:00 to 4:00 PM. Note that GSK will have this line open for your call any time after 2:45 PM.

Toll free number: 1 (888) 643-3083
Participant Passcode: 55020422

Please listen to the instructions to initiate this teleconference and enter the passcode and press # when prompted.

Additionally, you have my authorization to send me via e-mail any FDA correspondence related to this teleconference.

Kind regards,
Sue

Susan Spooner, Ph.D.
GlaxoSmithKline
CMC Regulatory Affairs
Phone: (919) 483-6199

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22465

ORIG-1

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/s/

DEBORAH M MESMER
09/11/2009

From: Mesmer, Deborah
Sent: Friday, September 04, 2009 5:57 PM
To: 'susan.p.spooner@gsk.com'
Subject: NDA 22-465 FDA comments for TCON on September 8, 2009

From: Deborah Mesmer, Regulatory Health Project Manager, ONDQA

To: Susan Spooner, Ph.D., Assistant Director, CMC Regulatory Affairs, GSK

Please refer to your NDA 22- 465 VOTRIENT™ (pazopanib hydrochloride) Tablet, 200 mg; 400 mg. We have the following comments pursuant to the teleconference meeting scheduled for Tuesday, September 8, 2009:

1. Provide the particle size distribution data using (b) (4) method for the batches with the dissolution profile data shown in Figures 24 and 25 (document "m3.2.P.2.3. Pharmaceutical Development_Manufacturing Process Development" in module 3 of the original submission).
2. Provide the complete dissolution data at all the time points for the three batches with different particle sizes shown in Figure 21 and Table 10 in the same document.
3. It is noted in your response to question 10c in the amendment to the NDA dated August 18, 2009, that use of a different source of magnesium stearate supplier (lot with high specific surface area) led to increased variability in dissolution. Include in the specification for magnesium stearate controls on specific surface area with appropriate acceptance criteria to minimize batch-to-batch variability in dissolution.

(b) (4)

(b) (4)

1)

Note that there may be some additional points of discussion at the meeting.

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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/s/

DEBORAH M MESMER
09/04/2009



NDA 22-465

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Ellen S. Cutler
Senior Director, US Regulatory Affairs
Oncology
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Cutler:

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

We also refer to your submissions dated June 5, 2009, June 24, 2009, July 17, 2009, and July 31, 2009, and the FDA minutes dated July 23, 2009, for the face-to-face Type C Chemistry, Manufacturing and Controls meeting held on July 1, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request that you respond by August 18, 2009, in order to continue our evaluation of your NDA.

(b) (4)

2. To provide assurance of optimum dissolution rate and secondary processing ability, as well as to reflect the range of particle sizes measured in your clinical trial batches, adopt the following acceptance criteria for particle size:

(b) (4)

Also refer to the FDA meeting minutes dated July 23, 2009, for the meeting held with GSK on July 1, 2009 for further discussion.

(b) (4)

The following comments pertain to *Comparability Protocol For Changes In Drug Substance* (b) (4) Sites.

4. The use of an Annual Report as a regulatory submission to inform the Agency of a change in (b) (4) site is unacceptable. Current GMP status must be confirmed by the CDER Office of Compliance prior to approval to use the proposed site. Modify the reporting vehicle to be used for reporting changes in (b) (4) sites to provide for use of a prior-approval supplement.

5. The following statement is both unclear and unsatisfactory in intent:

At least one batch of (b) (4) pazopanib hydrochloride from the alternate site meets approved specifications, including data demonstrating that the particle size distribution of drug substance (b) (4) at the alternate site meets the approved criteria for X_{10} , X_{50} and X_{90} .

a. Determining satisfactory performance by meeting specifications is inadequate. The data from the proposed site should be equivalent to that from the currently approved site.

b. Modify the above statement to clarify that all batches submitted (not just one) to support this site change must meet the requirements approved in this comparability protocol, and that data from all batch particle size distribution measurements, not just individual X_{10} , X_{50} and X_{90} data points, are equivalent to that produced at the currently approved site. Propose a definition of equivalency that will assure statistical significance.

The following comments pertain to drug product manufacturing:

6. Include (or revise) the following information in the P 3.3 section:

a. Batch size, since batch size is fixed for this process

b. (b) (4), since these are fixed for all batches

7. Remove the term "or validated equipment" for the (b) (4) since no data have been provided for batches manufactured with other equipment for these unit operations. (b) (4)

(b) (4)
there is no change in equipment type, construction, or location.

8. Provide details about any conducted manufacturing hold-time studies in the NDA (i.e. hold time studies for (b) (4) drug product quality (b) (4) Provide data to show that hold times have no adverse impact on (b) (4)

(b) (4)

(b) (4)



The following comments pertain to the amendment dated July 17, 2009, *Responses to FDA Comments Dated 11 June 2009*:

12. In your amendment dated July 17, 2009 the (b) (4) method described in the "Control of critical steps and intermediates" section is identical to the one submitted in the original application. Since the original (b) (4) d was significantly updated in the amendment dated June 5, 2009, please explain why did you revert to the original method.

The following comments pertain to the amendment dated July 31, 2009, *Responses to FDA Comments Dated 13 July 2009*:

13. In your cover letter, it was stated, "Responses 1b, 1c and 2 also include corresponding data which are provided in Excel format." However, we could not find the Excel files. Please identify where in the NDA this information is located, or provide it if not already included.
14. The file named, "batch-release-disso-profiles.xpt" seems to be the same as the stability dataset and contains half of the file of "pivotal-stability-data.xpt". Please provide the correct version.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope Miksinski
08/05/2009