CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-981

NAME OF APPLICANT / NDA HOLDER
SmithKline Beecham Corporation d/b/a GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Oral Hycamtin

ACTIVE INGREDIENT(S)	STRENGTH(S)
Topotecan hydrochloride	EQ 0.25mg topotecan (free base) EQ 1mg topotecan (free base)

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,004,758	4/2/1991	5/28/2010

d. Name of Patent Owner
SmithKline Beecham Corporation

Address *(of Patent Owner)*
Attn: Vice President, Corporate Intellectual Property
709 Swedeland Road
UW2220, P.O. Box 1539

City/State
King of Prussia, PA

ZIP Code	FAX Number *(if available)*
19406-0939	(610) 270-5090
Telephone Number	**E-Mail Address *(if available)***
(610) 270-5021	charles.m.kinzig@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes ☐ No

APPEARS THIS WAY
ON ORIGINAL

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 26 (Additional claims listed in Attachment)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Treatment of patients with relapsed small cell lung cancer	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Kathryn L. Sieburth	27 March 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Kathryn L. Sieburth	
Address GlaxoSmithKline 709 Swedeland Road. UW2220, P.O. Box 1539	City/State King of Prussia, PA
ZIP Code 19406-0939	Telephone Number (610) 270-5012
FAX Number *(if available)* (610) 270-5090	E-Mail Address *(if available)* kathryn.l.sieburth@gsk.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

. Method of Use (continued)

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 27	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	*Use (Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of patients with relapsed small cell lung cancer

4. Method of Use (continued)

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 28	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	*Use (Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of patients with relapsed small cell lung cancer

4. Method of Use (continued)

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 30	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	*Use (Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of patients with relapsed small cell lung cancer

. Method of Use (continued)

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 32	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	*Use (Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of patients with relapsed small cell lung cancer

4. Method of Use (continued)

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information.

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2 Patent Claim Number *(as listed in the patent)* 33	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	*Use (Submit indication or method of use information as identified specifically in the proposed labeling.)* Treatment of patients with relapsed small cell lung cancer

EXCLUSIVITY SUMMARY FOR NDA # 20-981 SUPPL # N/A

Trade Name: Oral HYCAMTIN (topotecan) Capsules
Generic Name: N/A

Applicant Name: SmithKline Beecham Corporation, d/b/a GlaxoSmithKline HFD#: 150

Approval Date If Known: October 11, 2007

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ 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 /_X_/ 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:
N/A

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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

___3 years___

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

YES /_X_/ NO /___/

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

_____NO_____

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 /_X_/

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 /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the

active moiety, and, if known, the NDA #(s).

NDA# 20-671 HYCAMTIN

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# _____ _____

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 NDA'S 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 /_X_/ 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 /_X__/ 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 /_X_/ 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 /_X_/

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 /_X_/

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:

Study 387 (Investigation# 1), Study 065 (Investigation# 2), Study 396 (Investigation# 3), and Study 478 (Investigation#4)

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 re-demonstrate 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 /_X__/
Investigation #2	YES /___/	NO-/__X_/
Investigation #3	YES /___/	NO /__X_/
Investigation #4	YES /___/	NO /__X_/

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

N/A	

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 /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/
Investigation #4	YES /___/	NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 387(Investigation# 1), Study 065(Investigation# 2)

Study 396(Investigation# 3), Study 478(Investigation# 4)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 42,993__ YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # 42,993_ YES /_X_/ NO /___/ Explain: _____

Investigation #3

IND # 42,993_ YES /_X_/ NO /___/ Explain: _____

Investigation #4

IND # N/A_ YES /__/ NO /_X_/ Explain: The pivotal Study 478 was not carried out under IND# 42,993.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #4 !

YES /_X__/ Explain _____ ! NO /___/ Explain:_____

GlaxoSmithKline did in fact certify that they provided substantial support for this study.

(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 /_X__/

If yes, explain: _____

Signature Kim J. Robertson Date: October 2, 2007
Title: Consumer Safety Officer

Signature of Office/: Robert L. Justice, M.D.
Division Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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
10/10/2007 01:17:51 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 20-981 Supplement Type (e.g. SE5): N/A Supplement Number: 000

Stamp Date: April 11, 2007 PDUFA Goal Date: October 11, 2007

HFD-150 Trade and generic names/dosage form: Oral HYCAMTIN® (topotecan) Capsules

Applicant: GlaxoSmithKline Therapeutic Class: 5010100

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

XX Yes. Please proceed to the next question.

☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): NONE

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Oral HYCAMTIN® (topotecan) Capsules are indicated for the treatment of patients with relapsed small cell lung cancer.

Is this an orphan indication?

☐ Yes. PREA does not apply. Skip to signature block.

XX No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

XX Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population

☐ Disease/condition does not exist in children

XX Too few children with disease to study

☐ There are safety concerns

☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Kim J. Robertson

{See appended electronic signature page}

Consumer Safety Officer

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

☐ **Yes. PREA does not apply. Skip to signature block.**

☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Kim J. Robertson, Consumer Safety Officer

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Kim Robertson
9/26/2007 12:43:53 PM
First page had an incorrect NDA number on it; this is the correct form; Pediatric Page for Oral HYCAMTIN

HYCAMTIN® (topotecan) Capsules for treatment of patients with
relapsed small cell lung cancer
NDA 20-981

DEBARMENT CERTIFICATION

GlaxoSmithKline 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.

Charles E. Mueller
Director, North America Clinical Compliance
Worldwide Regulatory Compliance

21 MAR 2007
Date

TELECON MINUTES

TELECON DATE: October 5, 2007 **TIME:** 11:00AM **LOCATION:** Room 2376

NDA: 20-981 **Meeting Request Submission Date:** October 2, 2007 (via e-mail)
FDA Response Date: October 3, 2007 (via e-mail)
Briefing Document Submission Date: N/A

DRUG: Oral HYCAMTIN® (topotecan) Capsules

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of TELECON: Labeling Discussions

PROPOSED INDICATION: This drug is indicated for the treatment of patients with relapsed small cell lung cancer.

FDA PARTICIPANTS:

Robert L. Justice, M.D., Division Director
Ramzi Dagher, M.D., Division Deputy Director *(Meeting Chair)*
Robert White, Jr., M.D.
Leigh Verbois, Ph.D., Pharmacology Supervisor
William D. McGuinn, Ph.D., Pharmacology Reviewer
Brian P. Booth, Ph.D., Clinical Pharmacology Team Leader
Chia-wen (Kiki) Ko, Ph.D., Statistical Reviewer
Kim Robertson, Consumer Safety Officer *(Minutes Recorder/Facilitator)*

GSK PARTICIPANTS:

Philip Witman, US Regulatory
Richard Swenson, Ph.D., US Regulatory
Robert Watson, US Regulatory
Deneen Stewart, Ph.D., US Regulatory
Dale Stockbower, US CMC Regulatory
Roya Behbahani, PharmD, US Labeling
Paul Wissel, M.D., Clinical
Philippe Legenne, M.D., Clinical
Christopher Abissi, M.D., Safety

GSK PARTICIPANTS (cont):

Charlotte Rosenthal, Safety
Bernie Bharan, Statistics
Deborah Smith, PharmD, Clinical Pharmacology
Maureen Neary, Ph.D., Global Health Outcomes
Michael Henry, Project Leader
Sharlene Cirillo, Ph.D., US Commercial

MEETING OBJECTIVES: To discuss suggested edits that both the FDA and GSK made to the Oral HYCAMTIN label.

BACKGROUND: On October 2, 2007, GlaxoSmithKline e-mailed the division to request a telecon to discuss the proposed modifications to their labeling for the New Drug Application for Oral HYCAMTIN® (topotecan) Capsules submitted to the Agency on April 11, 2007. Both the Agency and GlaxoSmithKline agreed that such a discussion would be more expeditious and productive.

DISCUSSION: The issues raised by GSK on their e-mail dated October 2, 2007 were discussed point by point.

ACTION ITEMS:

GSK will submit the following to their NDA: 1) a brief statement to be added to the Geriatric Use section of the labeling regarding efficacy in patients younger than 65 years of age and those 65 and older and justification for this statement, 2) analyses to support any claim regarding the use of [redacted] Oral HYCAMTIN, 3) revised labeling. b(4)

The FDA will forward DMETS input on the proposed tradename. The FDA will review revised labeling to be submitted as indicated above.

Kim Robertson
Consumer Safety Officer

Concurrence Chair:
Ramzi Dagher, M.D.
Deputy Director

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

/s/

Kim Robertson
10/9/2007 04:06:48 PM
CSO
05October07 NDA T-con Mtg. Mins.

Ramzi Dagher
10/10/2007 12:20:01 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **20-981** Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: **Oral HYCAMTIN® (topotecan) Capsules**
Established Name: **(topotecan)**
Strengths: **2.3 mg/m^2**

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

Date of Application: **April 11, 2007**
Date of Receipt: **April 11, 2007**
Date clock started after UN: N/A
Date of Filing Meeting: **June 8, 2007**
Filing Date: **June 22, 2007**
Action Goal Date (optional): **October 11, 2007** User Fee Goal Date: **October 11, 2007**

Indication(s) requested: **Oral HYCAMTIN® (topotecan) Capsules are indicated for the treatment of patients with relapsed small cell lung cancer.**

Type of Original NDA:	(b)(1) X	(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 X
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

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

User Fee Status: Paid X 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 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 X
  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 X

- 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 X

  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 X
  If yes, explain:

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

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

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

- Submission complete as required under 21 CFR 314.50? YES X 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 ☐
   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?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES NO ☐

   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 X 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- 3yrs Years NO ☐

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: 42,993
- 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) November 5, 1998; April 18, 2001; February 21, 2006 NO ☐

  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) September 12, 2002; September 12, 2006 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?
  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: October 4, 2007

NDA #: 20-981

DRUG NAMES: Oral HYCAMTIN® (topotecan) Capsules, 2.3 mg/m^2

APPLICANT: GlaxoSmithKline

BACKGROUND: GlaxoSmithKline has submitted an NDA for Oral HYCAMTIN® (topotecan) Capsules, a topoisomerase I inhibitor professing to be designed to relieve torsional strain in DNA by inducing reversible single strand breaks, by binding to the DNA complex and preventing relegation of these single strand breaks for patients with relapsed small cell lung cancer.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

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

Discipline/Organization	Reviewer
Medical:	Robert White, Jr., M.D.
Secondary Medical:	Ramzi Dagher, M.D.
Statistical:	Chia-wen (Kiki) Ko, Ph.D.; Rajeshwari Sridhara, Ph.D
Pharmacology:	William D. McGuinn, Ph.D; Leigh Verbois, Ph.D.
Statistical Pharmacology:	N/A
Chemistry:	Brian Rogers, Ph.D.; Ravindra Kasliwal, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sophia Abraham, Ph.D.; Brian Booth, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Dan-My Chu, Ph.D.
OPS:	N/A
Regulatory Project Management:	Kim J. Robertson, CSO
Other Consults:	DMETS, SEALD, DDMAC, DSI, DSRCS/OSE

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

CLINICAL FILE X REFUSE TO FILE ☐

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

- Advisory Committee Meeting needed? YES, date if known _____ NO X

- 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 X YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A	X	FILE	☐	REFUSE TO FILE	☐
STATISTICS	N/A	☐	FILE	X	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	☐

- Biopharm. study site audits(s) needed? ☐ NO X
  YES

PHARMACOLOGY/TOX	N/A	☐	FILE	X	REFUSE TO FILE	☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY			FILE	X	REFUSE TO FILE	☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES ☐ NO X
  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:

X 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.

X 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. X Convey document filing issues/no filing issues to applicant by Day 74.

Kim J. Robertson
Consumer Safety Officer

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

1. The new rule [21 CFR 201.57(a)(4) requires that the verbatim statement, *"See full prescribing information for complete boxed warning"* must be placed immediately following the heading of the Boxed Warning.

2. In the FPI: Contents section of your label, we note that you have the sub-heading 6.3, *Postmarketing Experience*; yet, in the actual FPI, there is no mention of a sub-heading 6.3, nor is there any content for 6.3. We also note that your sub-heading for 6.2 in the FPI is entitled, *Clinical Trials and Postmarketing Experience* with IV HYCAMTIN. The new rule [21 CFR 201.57(c)(7)] requires Postmarketing Experiences be presented separately from the listing of adverse reactions identified in clinical trials. Please refer to *Guidance for Industry, Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products—Content and Format*, Section III C.

   Please remove the first paragraph about reactions in the IV HYCAMTIN clinical trials from sub-heading 6.2 of the FPI and make it the last section under sub-heading 6.1 of the FPI; *Clinical Trials Experience.* With regard to sub-heading 6.2, please rename it, "Postmarketing Experience" and retain the remaining verbiage therein. Please then omit sub-heading 6.3 in your FPI: Contents and correct the title for 6.2 to "*Postmarketing Experience*".

3. Please remove the dashes for dosage strengths.

4. Please remove general information (e.g., GlaxoSmithKline's website) from the label.

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 Robertson
10/4/2007 02:15:19 PM
CSO
NDA Regulatory Filing Review

Dotti Pease
10/5/2007 08:15:15 AM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Drug Oncology Products

Application Number: NDA 20-981

Name of Drug: Oral HYCAMTIN® (topotecan) Capsules, 2.3 mg/m^2

Applicant: GlaxoSmithKline

Material Reviewed:

Submission Date(s): April 11, 2007

Receipt Date(s): April 11, 2007

Submission Date of Structure Product Labeling (SPL): April 11, 2007

Type of Labeling Reviewed: WORD

Background and Summary

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

Review

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

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

1. The new rule [21 CFR 201.57(a)(4) requires that the verbatim statement, *"See full prescribing information for complete boxed warning"* must be placed immediately following the heading of the Boxed Warning.

2. In the FPI: Contents section of your label, we note that you have the sub-heading 6.3, *Postmarketing Experience*; yet, in the actual FPI, there is no mention of a sub-heading 6.3, nor is there any content for 6.3. We also note that your sub-heading for 6.2 in the FPI is entitled, *Clinical Trials and Postmarketing Experience* with IV HYCAMTIN. The new rule [21 CFR 201.57(c)(7)] requires Postmarketing Experiences be presented separately from the listing of adverse reactions identified in clinical trials. Please refer to *Guidance for Industry, Adverse Reactions Section for Labeling for Human Prescription Drug and*

Biological Products—Content and Format, Section III C.

Please remove the first paragraph about reactions in the IV HYCAMTIN clinical trials from sub-heading 6.2 of the FPI and make it the last section under sub-heading 6.1 of the FPI; *Clinical Trials Experience.* With regard to sub-heading 6.2, please rename it, "Postmarketing Experience" and retain the remaining verbiage therein. Please then omit sub-heading 6.3 in your FPI: Contents and correct the title for 6.2 to "*Postmarketing Experience*".

3. Please remove the dashes for dosage strengths.

4. Please remove general information (e.g., GlaxoSmithKline's website) from the label.

Recommendations

Convey to applicant above deficiencies/issues in 74 day letter.

Subsequent to issuance of 74 day letter:

GlaxoSmithKline addressed the identified deficiencies/issues and re-submitted labeling on October 2, 2007.

I reviewed the October 2, 2007, resubmitted labeling and noted the inserted revisions as stated by the applicant. No additional issues/deficiencies were noted.

Kim J. Robertson
Consumer Safety Officer

Supervisory Comment/Concurrence:

Dotti Pease
Chief, Project Management Staff

Drafted: KJR/October 3, 2007
Revised/Initialed: dp/10.3.07
Finalized: DPease/ 10.3.07
Filename: C:\cso\Robertson\NDA's\20981\PM Labeling Review
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Kim Robertson
10/3/2007 01:11:59 PM
CSO
PM/PLR Labeling Review NDA 20981

Dotti Pease
10/4/2007 01:17:10 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-981

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Attention: Philip A. Witman, M.P.H., M.Phil.
Associate Director, US Regulatory Affairs, Oncology

Dear Mr. Witman:

Please refer to your April 11, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oral HYCAMTIN® Capsules (topotecan), 0.25 mg; 1.0 mg received April 11, 2007.

In our filing review, we have identified the following potential review issues:

1. The new rule [21 CFR 201.57(a)(4) requires that the verbatim statement, *"See full prescribing information for complete boxed warning"* must be placed immediately following the heading of the Boxed Warning.

2. In the FPI: Contents section of your label, we note that you have the sub-heading 6.3, *Postmarketing Experience*; yet, in the actual FPI, there is no mention of a sub-heading 6.3, nor is there any content for 6.3. We also note that your sub-heading for 6.2 in the FPI is entitled, *Clinical Trials and Postmarketing Experience* with IV HYCAMTIN. The new rule [21 CFR 201.57(c)(7)] requires Postmarketing Experiences be presented separately from the listing of adverse reactions identified in clinical trials. Please refer to *Guidance for Industry, Adverse Reactions Section for Labeling for Human Prescription Drug and Biological Products—Content and Format*, Section III C.

   Please remove the first paragraph about reactions in the IV HYCAMTIN clinical trials from sub-heading 6.2 of the FPI and make it the last section under sub-heading 6.1 of the FPI; *Clinical Trials Experience.* With regard to sub-heading 6.2, please rename it, "Postmarketing Experience" and retain the remaining verbiage therein. Please then omit sub-heading 6.3 in your FPI: Contents and correct the title for 6.2 to "*Postmarketing Experience*".

3. Please remove the dashes for dosage strengths.

4. Please remove general information (e.g., GlaxoSmithKline's website) from the label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Ann Farrell
6/22/2007 04:01:21 PM
Farrell for Justice

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-981

NDA ACKNOWLEDGMENT

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Attention: Philip A. Witman, M.P.H., M.Phil.
Associate Director, US Regulatory Affairs

Dear Mr. Witman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Oral HYCAMTIN® (topotecan) Capsules, 0.25mg and 1mg

Review Priority Classification: Priority

Date of Application: April 11, 2007

Date of Receipt: April 11, 2007

Our Reference Number: NDA 20-981

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 11, 2007 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 11, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a waiver of pediatric studies for this application and have waived the pediatric study requirement for this application. We also acknowledge receipt of your request for exemption from the four-month safety update for this application. Your request for exemption from the four-month safety update for this application has been granted.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Consumer Safety Officer
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/

Kim Robertson
6/11/2007 03:57:18 PM
60 Day NDA Ack Letter

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(White Oak 22; Mail Stop 4447)

DATE RECEIVED: 8/27/2007 **DATE OF DOCUMENT:** 4/11/2007	**DESIRED COMPLETION DATE:** 9/11/2007 **PDUFA:** 10/11/2007	**OSE REVIEW #:** 2007-1851

TO: Robert Justice, MD
Director, Division of Drug Oncology Products, HFD-150

THROUGH: Kellie Taylor, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Judy Park, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Oral HYCAMTIN®** (Topotecan) Capsules 0.25 mg and 1 mg **NDA #:** 20-981	**SPONSOR:** GlaxoSmithKline

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Oral Hycamtin. We specifically object to the use of "Oral" in the name. We believe this oral formulation could be managed under the name, Hycamtin, which we find acceptable.

2. DDMAC finds the proprietary name, Oral Hycamtin, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Sam Chan, OSE Project Manager, at 301-796-2283.

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE
Caroline Gilmore
ONE FRANKLIN PLAZA 16TH AND RACE STREETS
PHILADELPHIA PA 19101
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

20-981

2. TELEPHONE NUMBER
919-483-0696

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Oral Hycamtin Capsules (topotecan)

6. USER FEE I.D. NUMBER
PD3007152

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Craig A. Metz	VP-US Regulatory	3/22/07

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$896,200.00

Form FDA 3397 (12/03)

Close Print Cover sheet

MEETING MINUTES

DATE: September 12, 2006 **TIME:** 11:30AM **LOCATION:** Room 2201

IND/NDA: IND: 42,993 **Meeting Request Submission Date:** June 15, 2006
FDA Response Date: June 29, 2006
Briefing Document Submission Date: August 15, 2006

DRUG: HYCAMTIN® (topotecan hydrochloride) Oral Capsules

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of MEETING: Pre-NDA

Proposed Indication: To use Oral Topotecan Hydrochloride as treatment of patients with relapsed small cell lung cancer after failure of first-line therapy.

FDA PARTICIPANTS:

Robert L. Justice, M.D., Div. Director
Ann Farrell, M.D., Acting Div. Deputy Director
Ramzi Dagher, M.D., Clinical Team Leader *(Meeting Chair)*
Michael Brave, M.D. Clinical Reviewer
Raji Sridhara, Ph.D., Statistical Team Leader
Chia-wen (Kiki) Ko, Ph.D., Statistical Reviewer
Kim Robertson, Consumer Safety Officer *(Minutes Recorder/Facilitator)*

GLAXOSMITHKLINE PARTICIPANTS:

Bernie Dharan, MS, Senior Statistician, Biomedical Data Sciences
Sesha Reddigari, Ph.D., Lead Clin Development Scientist, Oncology Medicine Development Ctr.
Paul Wissell, M.D., Group Director, Oncology Medicine Development Center
Michael Henry, MS, Project Leader, Oncology Project Management
Philip Whitman, MPH, MPhil, Associate Director, US Regulatory Affairs, Oncology
Robert Watson, MBA, Vice President, US Regulatory Affairs, Oncology

BACKGROUND:

GlaxoSmithKline (GSK) requested this Pre-NDA Meeting for oral topotecan as treatment of patients with relapsed small cell lung cancer (SCLC) after failure of first-line therapy. Intravenous (IV) topotecan is currently approved as a single agent for treatment of patients with SCLC sensitive disease after failure of initial or subsequent chemotherapy, defined as having responded to but subsequently progressing at least 60 to 90 days after completion of chemotherapy. No other drug or drug combination has been approved for patients with relapsed SCLC.

In support of this application, GSK proposes to submit data from four randomized clinical studies in which one arm received single agent oral topotecan 2.3 mg/m^2 daily x 5 q 21 days. These include three efficacy studies in SCLC (478, 065, and 396) and one safety study in non-small cell lung cancer (387).

Table 1. Proposed registration studies

Study	Population	N	Design	1^O endpoint
478	Relapsed sensitive SCLC	71	Oral T vs. BSC	Median OS
065	Relapsed sensitive SCLC	52	Oral vs. IV T	ORR (superiority)
396	Relapsed sensitive SCLC	153	Oral vs. IV T	ORR (noninferiority)
387	Pre-treated advanced NSCLC	407	Oral T vs. docetaxel	OS at 1-year

The median number of oral topotecan cycles received per patient was 4 in the SCLC studies and 3 in the NSCLC study. The primary endpoint for Study 478 was overall survival (OS). The primary endpoint for Studies 065 and 396 was overall response rate (ORR) and for Study 387 was OS at 1 year.

In Study 478, median OS in the oral topotecan arm was superior to that of patients receiving best supportive care (25.9 months vs. 13.9 months; log-rank p = 0.0104). In Studies 065 and 396, ORRs were not statistically different between arms; however, GSK proposes to pool those results and show by noninferiority analysis that the ORR of oral topotecan is within 10% of that of the IV formulation.

The incidence of toxic deaths among patients treated with oral topotecan was comparable to that among patients with IV topotecan or docetaxel. Hematologic toxicity was dose limiting and generally comparable to that of IV topotecan or docetaxel. The incidences of nausea and vomiting were higher than with IV topotecan or docetaxel, whereas the incidences of diarrhea and stomatitis were slightly lower.

HYCAMTIN® (topotecan hydrochloride) Oral Capsules
IND 42,993; NDA 20-981

Pre-NDA Meeting (Second Line Small Cell Lung Cancer)
September 12, 2006

Attachment 5: Questions for the FDA

We respectfully request the Division's detailed responses to the questions that are summarized below.

Oral HYCAMTIN has been studied in several cancer settings at different doses and schedules, either as monotherapy or in combination with other agents. Three of these studies (GSK studies 478, 065, and 396) were conducted in patients with relapsed small cell lung cancer (SCLC). An additional study (387) was conducted in patients with relapsed advanced non-small cell lung cancer (NSCLC). In these four studies, 690 patients were randomized to receive, and 682 patients received, oral HYCAMTIN monotherapy at the proposed regimen of 2.3 mg/m^2/day for five consecutive days, every 21 days. Tables 2-4 of the Clinical Summary (Attachment 3) of this Briefing Document describe the studies to be included in the NDA with proposals for how these studies will be reported.

We feel that the NDA will provide substantial evidence to support the proposed indication:

> **HYCAMTIN capsules are indicated for the treatment of patients with relapsed small cell lung cancer after failure of first-line therapy.**

Questions Related to Clinical Efficacy

The planned format of the efficacy summary will be to present the study results of studies 478, 065, and 396 individually, as well as a combined meta-analysis of overall survival and response rate endpoints for the supportive studies 065 and 396.

1. Does the FDA agree that the primary study (study 478) along with the supporting studies (065 and 396), as designed, provide adequate basis to support the activity and clinical benefit of oral HYCAMTIN, when given as **monotherapy at 2.3 mg/m^2/day for five consecutive days every 21 days**, in the second line setting for patients with SCLC and would support an indication as proposed?

FDA Response:

Potentially. The apparent improvement in OS as described for Study 478 could be the basis for an approval pending review.

The acceptability of these studies to support the specific wording proposed for the indication would be a review issue (see also #12).

Please clarify whether response and TTP were assessed in the BSC arm of Study 478. Please provide the results if they were assessed.

GlaxoSmithKline Comment (9/11/06): ↓

Neither tumor response nor TTP were assessed in the BSC arm of Study 478. From Page 30 of the Briefing Document: "For patients in the BSC alone arm, radiological assessment of tumor response was not justified, as the predicted response rate was zero." On Page 33: "TTP was not assessed for patients in the BSC alone arm of study 478 because radiologic assessment for clinical progression was not required for that arm."

Discussion Point: Because of the differential assessment of response and TTP in the two treatment arms of Study 478 specifically, response and TTP would not be considered supportive secondary endpoints and would not be included in the labeling.

2. Does the FDA agree that the primary endpoint of overall survival in study 478 sufficiently demonstrates the clinical benefit of oral HYCAMTIN in the proposed indication?

FDA Response: Please see #1.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

3. Does the FDA agree that the two supporting efficacy studies (065 and 396) that demonstrate clinical benefit between oral HYCAMTIN and IV HYCAMTIN in terms of survival, response rate, and improvement in symptoms related to SCLC are appropriate as supportive studies for this indication?

FDA Response: These studies may be appropriate to lend support to your application. However, we do not agree that they "demonstrate clinical benefit between oral HYCAMTIN and IV HYCAMTIN in terms of survival, response rate, and improvement in symptoms related to SCLC" for the following reasons.

GlaxoSmithKline Comment (9/11/06): ↓

In reading the FDA response, we recognize that the question may not have expressed our original intent, and we apologize for the lack of clarity. Our intent was not to compare the two formulations in terms of superiority, but rather that oral HYCAMTIN gives similar efficacy results compared to IV HYCAMTIN in this same patient population.

a. **Clinical benefit is generally understood as that which improves the quantity or quality of life. Tumor response in this setting is generally not regarded as clinical benefit in and of itself.**

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

b. **You state that these studies did *not* show improvement in progression-free or overall survival as compared to IV topotecan.**

GlaxoSmithKline Comment (9/11/06): ↓

This is correct. Studies 065 and 396 were not designed to show superiority of progression-free survival or overall survival of the oral formulation to the IV formulation. These studies were conducted to show similarity in the primary endpoint of response rate between two routes of administration of the same drug. We feel that the data from studies 065 and 396 support this objective.

Discussion Point: FDA considers comparisons of the IV and oral formulations to be exploratory. The sponsor considers Study 396 to be pre-specified as a non-inferiority study with respect to response rate.

c. **Quality of life is not interpretable in unblinded trials.**

GlaxoSmithKline Comment (9/11/06): ↓

We request clarification of this statement for our knowledge and future drug development. In particular, we would like clarification as to the current FDA position about symptom assessments and quality of life.

Discussion Point: FDA referred sponsor to the draft PRO guidance which is available on the web. In addition, the sponsor was encouraged to meet with the division and the SEALD group for future drug development plans using PROs.

d. Whether the results of Study 065 or 396 will be included in the labeling is a review issue.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

4. The Agency had found it acceptable to combine the efficacy results of studies 065 and 396 in a meta-analysis at the Pre-NDA meeting for second line SCLC in September 2002.

   Is the FDA still in agreement with this proposed meta-analysis approach for studies 065 and 396 as supportive evidence of clinical benefit of oral HYCAMTIN in second line SCLC?

FDA Response:

Since these two studies have identical design features, combining the efficacy results is acceptable as an exploratory analysis. However, the efficacy results for IV HYCAMTIN appear to be quite different between studies 065 and 396. Do you have explanations?

It is unlikely that the meta-analysis results will be included in the label.

GlaxoSmithKline Comment (9/11/06): ↓

We do not feel that the results are quite different, as they are consistent with normal trial-to-trial variability based on clinical variance of patients. It is not unreasonable to expect differences in efficacy between a small Phase II study and a large Phase III study. The variability in response rates and survival was larger in the IV arm, and was more consistent in the oral arm that is the focus of this proposed application. The sample size of the 396 study was approximately three times larger than in study 065. As the studies have identical design features, a meta-analysis would give more precise estimates. We have no further explanations at this time; this will be addressed in the application.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

5. Attachment 3 contains an outline of the overall statistical analysis plan for the proposed NDA.

   Does the FDA agree with the remainder of the analysis plan as described in this section?

FDA Response:

The proposed analysis plan appears acceptable for Study 478. Please clarify the following issues:

1. **Were response rate and time to progression data collected in BSC arm in primary study?**

GlaxoSmithKline Comment (9/11/06): ↓

As indicated in the response for Question 1, neither tumor response nor TTP were assessed in the BSC arm of Study 478.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

2. **Different endpoint definitions (due to different ITT definition):**
   a. **survival – time from the randomization date (in study 478) or the first dose of study medication (in studies 065 and 396) to death**
   b. **response rate – denominator as randomized (in study 478) or treated (in studies 065 and 396) patients**

GlaxoSmithKline Comment (9/11/06): ↓

Studies 065 and 396 were conducted prior to 2001, and 478 was conducted after 2002. GSK had defined the ITT population for studies 065 and 396 to be consistent with the ITT population defined for previous IV HYCAMTIN studies. Subsequently, GSK changed the definitions used in the study 478 protocol to comply with the proposed FDA guidance to determine ITT populations. One of the analyses to be provided in the NDA will conduct a *post hoc* assessment of survival using the date of randomization in studies 065 and 396 in order to provide a more consistent comparison. However, we expect that this new analysis will not change the existing results in any appreciable way.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

3. **QoL endpoints in open label studies are not interpretable. Furthermore:**
    a. **Different QoL instruments were used (study 478: PSA and EQ-5D; study 065: PSA; study 396: FACT-L).**
    b. **Multiple symptoms/dimensions were evaluated without adjustment for multiple comparisons.**

6. In the primary study for efficacy (study 478), overall survival was the primary endpoint; response rate was a secondary endpoint and was assessed by the investigators. For patients in the Best Supportive Care alone arm, radiological assessment of tumor response was not justified as the predicted response rate was zero.

   In the supportive studies (065 and 396), response rate was the primary endpoint, and the responses were assessed by independent radiological review.

   Radiological assessments from these studies were collected on film and are not available in digital format.

   Will the FDA requests copies of the radiographic assessments to evaluate responses?

FDA Response: No, tumor measurements submitted in the raw datasets will be adequate. Please also see above.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

If Yes, are the actual scans acceptable?

FDA Response: Please see FDA response to the first portion of this question.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

<u>Questions Related to Clinical Safety</u>

Descriptions of the studies with oral HYCAMTIN that will be included in the NDA are found in Tables 2-4 of Attachment 3, the Clinical Summary.

Seven Phase I trials were conducted with oral HYCAMTIN as a **single agent** (Table 2); 312 patients were enrolled in these studies, and 209 of these patients received a dose of 2.3 mg/m^2/day. Patients in these studies were recruited from a variety of cancer indications.

Ten Phase II/III trials were conducted with oral HYCAMTIN as a **single agent in first and second line treatment of** various **cancer** indications (Table 3); 1142 patients received oral HYCAMTIN in these studies, and 1051 of these patients received a dose of 2.3 mg/m^2/day. The primary efficacy and safety studies (478, 065, 396, and 387) were four of these ten studies.

Six studies (Phase I, II, and III) studied oral HYCAMTIN as part of **combination regimens** in various cancer indications (Table 4); although 694 patients received oral HYCAMTIN in these studies, only 56 of these patients received a dose of 2.3 mg/m^2/day.

7. GSK proposes to submit integrated safety information from the four studies (478, 065, 396, and 387) in patients with lung cancer (SCLC and NSCLC) who received oral HYCAMTIN monotherapy at the proposed dose and schedule for second line treatment as the basis for the Summary of Clinical Safety. The number of patients who received oral HYCAMTIN in these studies is 682.

   Does the FDA agree with GSK's proposal?

FDA Response: Yes, assuming that individual safety datasets and analyses for Study 478 will be submitted.

GlaxoSmithKline Comment (9/11/06): ↓

Yes, GSK intends to submit the following datasets:
- **Individual safety datasets for Study 478**
- **Integrated safety datasets for Studies 065 and 396**
- **Summary of Clinical Safety (to include the oral HYCAMTIN safety data from studies 478, 065, 396, and 387).**

We request confirmation that FDA does not require individual safety datasets for studies 065, 396, and 387.

Discussion Point: FDA would prefer for the safety datasets for Study 478 to be separate from the other studies. The sponsor clarified the dataset for Study 387 will be included in the safety dataset containing all four studies. The individual datasets for Study 065, 396 and 387 will be available in an integrated safety dataset.

8. GSK proposes to submit listings of all serious adverse events and deaths within 30 days following treatment (excluding progressive disease) from all patients who received oral HYCAMTIN as monotherapy. In addition, there were six studies where oral

HYCAMTIN was used in combination with other chemotherapeutic agents; these are listed in Table 4 of the Clinical Summary (Attachment 3). GSK proposes to provide listings from these combination studies to the FDA upon request.

Does the FDA agree with GSK's proposal?

FDA Response: No. Your dataset(s) of all serious adverse events and deaths within 30 days following treatment for all patients who received oral HYCAMTIN as monotherapy should include events which the investigator attributed to progressive disease. These dataset(s) should contain a column or columns designating attribution so that events may be analyzed by attribution subsets.

GlaxoSmithKline Comment (9/11/06): ↓

GSK agrees, and will provide all information available for monotherapy studies from our SAE (OCEANS) database, including patients who died within 30 days following treatment due to progressive disease. The OCEANS database includes all GSK R&D studies. GSK will include a column to designate relationship to study medication as attributed by the Investigator.

In addition, there are a number of studies using oral HYCAMTIN that are not sponsored by GSK R&D (e.g., investigator initiated studies, cooperative group studies). We propose to not include these in the listings of all SAEs.

GSK further requests clarification that FDA agrees with our proposal to not include the six combination studies in the NDA.

Please note that GSK will provide listing from the OCEANS database, rather that datasets as described in the FDA response. GSK requests clarification from the FDA that patient listings will suffice instead of datasets.

Discussion Point: FDA requests that the sponsor summarize the populations and treatments used in the investigator initiated studies, cooperative group studies, and combination studies in order to prioritize the need for separate datasets for these studies. GSK will follow up with a telecon to determine the need for inclusion of this information in the NDA. The FDA requested datasets be provided in SAS transport format.

9. GSK proposes to submit case report forms (CRFs) and case narratives for deaths that occurred due to events other than disease progression, as well as CRFs and case narratives for patients whose adverse events resulted in discontinuation from the study within 30 days following the final dose of study medication, **only** from the pivotal studies

that support the second line SCLC indication (studies 478, 065, and 396). GSK proposes to provide CRFs and narratives on patients from other studies to the FDA upon request.

Does the FDA agree with GSK's proposal?

FDA Response: Yes. At the time the application is submitted, please provide CRFs for each patient who died during the study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving BSC, for each study which you intend to support safety or efficacy, per 21CFR§ 314.50(f)(2).

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

Questions Related to the Format of the NDA

GSK proposes to submit this NDA as an electronic submission in CTD format with Clinical Summaries of Safety and Efficacy in Module 2, as per ICH Guidance M4S and M4E. These summaries will contain all the information normally contained in an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS); thus, no separate ISE or ISS will be included in this submission.

10. Does the FDA agree that there is no need for any paper copies of the submission and that the submission of this NDA in an entirely electronic CTD format is acceptable?

FDA Response: Yes.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

11. Does the FDA agree that there is no need to include a separate Integrated Summary of Efficacy or Integrated Summary of Safety if the data contained in these sections is captured in Module 2 as part of the Clinical Summaries of Efficacy and Safety?

FDA Response: Yes.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

Miscellaneous Questions

12. If the NDA review is successful, does the Agency agree in principle that the following new indication would be appropriate?

    "**HYCAMTIN (topotecan hydrochloride) capsules are indicated for the treatment of patients with relapsed small cell lung cancer after failure of first-line therapy.**"

FDA Response: The specific wording of the indication will be a review issue and will depend on the study design, patient populations enrolled and results.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

13. Does the FDA agree that since the clinical studies that will comprise primary basis for the Summary of Clinical Safety were completed in 2003, and hence no new safety information is expected, an exemption may be granted from the submission of the four month safety update, per 21 CFR 314.50(d)(5)(vi)(b)?

FDA Response: Yes.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

14. HYCAMTIN (topotecan hydrochloride) for Injection was granted pediatric exclusivity on November 20, 2002, and therefore has met the requirements of the Pediatric Research Equity Act (PREA). Further, diagnosis of the proposed indication, SCLC, is extremely rare in patients younger than 40 years of age; thus; pediatric use of oral HYCAMTIN for SCLC is unlikely.

    Per Section VI(B)(1)(a) of the September 2005 Guidance for Industry entitled "*How to Comply with the Pediatric Research Equity Act*," a full waiver may be requested and granted if the necessary studies are impossible or highly impracticable to conduct. One qualifying example given is if the indication has extremely limited applicability to pediatric patients because the pathophysiology of the disease occurs for the most part in the adult population. The epidemiology of SCLC satisfies these criteria of Section 505B(a)(4)(A) of the Act. Thus, GSK requests that a waiver be granted for the conduct of separate pediatric studies for oral HYCAMTIN.

    Does the FDA agree that a full waiver from the conduct of separate pediatric studies for oral HYCAMTIN may be granted?

FDA Response: Yes.

Discussion Point: The sponsor did not need further discussion regarding the Agency's response.

Concurrence:

Kim Robertson
Consumer Safety Officer
Minutes Recorder/Facilitator

Ramzi Dagher, MD
Clinical Team Leader
Meeting Chair

Meeting Concluded at: 12:25PM

OTHER FDA COMMENTS:

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

4. PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-#1 Mo.		>1 Mo.-# 2Year		>2-#12	
	12-16		17-64		≤65	
Race:	White		Black		Asian	
	Other					

QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

Office of Surveillance and Epidemiology (OSE) Bullets

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to

engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

  Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

  Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>

  Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: http://www.fda.gov/cder/guidance/6359OCC.htm

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

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/s/

Ramzi Dagher
9/28/2006 11:00:50 AM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 17, 2007

TO: Kim Robertson, Regulatory Project Manager
Robert M. White Jr., MD, Medical Reviewer
Division of Oncology Drug Products

THROUGH: Joseph Salewski
Acting Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dan-My T. Chu, PhD
Regulatory Review Officer
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 20-981

NME: No

APPLICANT: GlaxoSmithKline

DRUG: Hycamtin (topotecan)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of relapsed, resistant small cell lung cancer.

CONSULTATION REQUEST DATE: July 6, 2007

DIVISION ACTION GOAL DATE: September 17, 2007

PDUFA DATE: October 11, 2007

I. BACKGROUND:

GlaxoSmithKline submitted a New Drug Application 20-981 for Hycamtin (topotecan) for the treatment of relapsed, resistant small cell lung cancer. This NDA will greatly expand the indication for this drug to include use of the drug as a treatment for relapsed, resistant small cell lung cancer. In addition, this NDA supports a new formulation that will be given orally and not via the current approved IV injection route of administration.

The review division specifically called DSI and requested these inspections because only foreign data are submitted in support of this application. The site in Bulgaria was specially chosen because it had a large number of subjects enrolled in the study. The sites in Croatia, Romania, the United Kingdom and the Ukraine were chosen due to concerns the medical officer had with possible conflicts of interest in that investigators for this study also served as authors on study publications related to this study. Study SK&F-104864/478 "An Open-Label, Randomised, Phase III Comparator Study of Active Symptom Control alone or in Combination with Oral Topotecan in Patients with Relapsed Resistant SCLC" was audited at all sites.

II. RESULTS (by protocol/site):

Name of CI and site #,	City	Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
Center : 072 Prof. Hristo Tsekov University Multiprofile Hospital for Active Treatment St. Marina, Varna, 9000, Bulgaria Tel: 011-359-52-302-894 E-mail:	Varna	Bulgaria	478	8/20-24/2007	Pending	Pending
Center: 08 Dr. Branka Cucevic University Hospital for Lung Diseases "Jordanovac" Zagreb, Croatia Cellular telephone: E-mail:	Zagreb	Croatia	478	8/20-24/2007	Pending	Pending
Center: 101 Dr. Tudor-Eliade Ciuleanu "I. Chiricuta" Institute of Oncology Cluj Napoca, 400015, Romania Tel: 011-40-264-598-361 E-mail:	Napoca	Romania	478	8/27-31/2007	Pending	Pending
Center: 042 Dr. Mary O'Brien Royal Marsden Hospital Department of Medicine Downs Road Sutton, Surrey, UK Tel: 011-44-20-8642-6011 E-mail: Mary.O'Brien@rmh.nhs.uk	Surrey	UK	478	9/3-7/2007	Pending	Pending

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Name of CI and site #,	City	Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
Center: 092 Prof. Yaroslav V. Shparyk State Regional Oncology Medical and Diagnostic Centre Department of Chemotherapy 2A Hashek Street Lviv, 79031, Ukraine Tel: 011-380-322-23-09-72 Fax: 011-380-322-23-07-67 E-mail: [redacted] et	Lviv	Ukraine	478	9/3-7/2007	Pending	Pending

b(6)

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Study SK&F-104864/478: This was an open label, multicenter, randomized, stratified, phase III study to evaluate the survival benefit to patients with resistant small cell lung cancer (SCLC) of receiving treatment with oral topotecan in addition to palliative active symptom control (ASC).

Primary objective: To compare the overall survival between patients with resistant SCLC who received ASC alone with those who received ASC in combination with oral topotecan.

Efficacy Parameters:
Primary Efficacy Endpoint - Survival
Secondary Efficacy Endpoint - Response Rate, Time to progression, patient symptom assessment (i.e. Effect on Disease Symptom Score and Quality of Life index)

After written informed consent was obtained, eligibility into the study was examined (Sec 4.2-4.3). Eligible patients were to (1) have relapsed SCLC following first-line chemotherapy, (2) be considered to be resistant to the first-line regiment, (3) not be considered candidates for further intravenous chemotherapy, (4) have a performance status of ≤ 2 and (5) be confirmed to have adequate bone marrow reserve to tolerate treatment with oral topotecan. Thus, prior to randomization, specific study procedures were to be performed (Sec 5.3.1-5.3.2). Once eligibility was confirmed, patients were randomized to receive either palliative care through active symptom control (ASC) alone or to ASC and treatment with oral topotecan 2.3mg/m^2/day administered for 5 consecutive days and repeated every 21 days. Patients randomized to the ASC arm were to be treated using only the medical procedures or medications defined in section 5.3.3. Specific study related procedures for patients randomized to ASC alone are described in Sec 5.4.3. Patients randomized to ASC and oral topotecan arm were to have management of their symptoms and/or treatment with oral topotecan continued, as long as it was in the patient's best interest to do so. Specific study procedures and possible dose modifications for subjects randomized to the oral topotecan arm were to be done according to the schedule described in Sec 5.4.1-5.4.2.

Note that for patients randomized to receive ASC alone, radiological assessment of tumour response was not to be done. Thus radiological assessment of apparent response was only to be done for patients randomized to receive oral topotecan. Also, radiological assessment is only required after 3 courses of treatment, in the absence of any signs or symptoms of progressive disease, and thereafter only to confirm an apparent response or if clinically indicated to confirm disease progression.

Inspected:

1. Center : 072
   Prof. Hristo Tsekov
   University Multiprofile Hospital for Active Treatment
   St. Marina, Varna, 9000, Bulgaria

   a. An audit of 13 out of 13 randomized subject records was conducted at this site.

   b. Limitations of inspection: Records are in foreign language.

   c. No 483 was issued to this site. The review division medical officer had requested that the field investigator examine specific additional information for each of the sites to be inspected. The field investigator sent responses to this additional information for the audit of this site and this information has previously been forwarded to the review division medical officer. In review of the information provided by the field, DSI notes the following:

      i. The investigator did not follow the investigational plan [21 CFR 312.60].

         1. The protocol specified that to be enrolled into the study, subjects were to have relapsed, resistant disease and thus not be candidates for further intravenous chemotherapy. Subject #78 (85500) was noted to have received post study chemotherapy (CAV regimen - armorubicin, cyclophosphamid, and vincristin) which the site claimed to be given to the subject to improve the subject's quality of life when the subject became sick several months after the completion of the study.

         2. The protocol specified that subjects were to receive an ECG at the screening visit and after the final course only, unless clinically indicated. Subject 134 (11202), randomized to the oral topotecan arm, did not receive the protocol specified ECG after the last course of treatment. While the written study procedures do not detail that subjects randomized to active symptom control arm were to receive a final ECG, it is noted this contradicts the outline flowsheet of the study cycle procedures which appears to show that an ECG was to be performed at screening and after final course only for all subjects. Final course could be loosely defined as final course of active symptom control measures for subjects randomized to that arm of the study. In that sense subjects 73(85489),124 (11200), and 121(11223), also did not receive the protocol specified ECG.

         3. The protocol specified that specific laboratory procedures were to be performed on day 8 of each cycle for subjects randomized to the oral topotecan arm. The day 8 protocol specific laboratory results were missing for cycles 3-5 for subject 127.

   Observations noted above are based on the communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

   d. Assessment of data integrity: The majority of the efficacy data generated by this site may be used in support of the respective indication. However, the review division should consider whether the subject #78 receiving post study chemotherapy contradicts with the eligibility criteria whereby only subjects with relapsed resistant disease were to be enrolled into the study. In addition, DSI would recommend the review division determine the impact on the safety of the drug for subjects noted above that did not have final ECGs performed and for subject #127 whose day 8 labs were missing for cycles 3-5.

2. Center: 08
Dr. Branka Cucevic
University Hospital for Lung Diseases "Jordanovac"
Zagreb, Croatia

a. At this site, 8 subjects were randomized into the study. An audit of 7 randomized subjects was conducted at this site.

b. Limitations of inspection: Records were in a foreign language.

c. The following were deviations noted at this site:

i. The investigator did not follow the investigational plan [21 CFR 312.60]. Specifically,

1. Several protocol deviations were noted for Subject # 508 including (a) subject did not meet the inclusion criterion that required that there be documented relapse of limited or extensive SCLC at least 45 days after the cessation of first-line therapy, which was indicative of resistant disease. Source records showed that only 28 days lapsed after cessation of first – line therapy prior to relapse; (b) Concomitant medications taken on November 29-30, 2003 (loperamide and tramadol) were not listed on a data clarification form sent to the site in June 2004; and (c) Blood chemistries were not taken as required by the protocol. Specifically during cycle one, day 15, subject #508's had abnormal glucose and GGT levels. These abnormal Glucose and GGT levels were not examined on day 1 of cycle 2 as required by the protocol.

2. The protocol specified that the study medication was to be stored between 2-8°C. There were no records to verify which thermometer was used to monitor the refrigeration temperature or whether the thermometers found at the site were appropriately calibrated. In addition, the pharmacy refrigerator did not have a temperature log designating the actual value of the refrigerator temperature during each day of the study; thus it could not be verified that the study medication was stored appropriately during the time of the study.

3. The protocol specified that to be enrolled into the study, subjects were to have relapsed, resistant disease and thus not be candidates for further intravenous chemotherapy. Subject #502 was noted to have received post study chemotherapy (Carboplatin &Etoposide).

ii The investigator did not prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)].

a. Source documents used to calculate creatinine clearance were not retained by the investigator. The field investigator calculated the creatinine clearance using the formula noted in the protocol for subject #509 and found that the creatinine clearance should have been 83.7; however the CRF dated October 3, 2003, reported that the creatinine clearance was 72.

b. Medical records for subject #501 showed that chemotherapy ended on August 28, 2001; however, the CRF shows the last dose of chemotherapy was on August 23, 2001.

c. Medical records for subject #505 showed that the last dose of first line chemotherapy (etoposide) was on April 13, 2003; however, the corresponding CRF indicates the last dose of etoposide was on April 11, 2003.

e. Discrepancies were noted between source documents and data clarifications sent to the site for the toxicity grades for subject #503 with respect to GGT levels. Source documents showed that the subject experienced a Grade 1 [56-137] GGT toxicity levels on June 15, 2002 (104), July 1, 2002 (64), and July 6, 2002 (58) and a Grade 2 [138-275] GGT toxicity on June 10, 2002 (185). These were inaccurately reported on data clarification forms sent to the site.

f. Discrepancies were noted in research records for subject #505 in relation to hypokalemia toxicity. A laboratory source document and CRF showed that the subject experienced a grade 3 hypokalemia toxicity on June 20, 2003; however, data query subsequently sent to the site noted that the hypokalemia toxicity was grade 2.

g. White-out was used for multiple corrections in the medical records.

iii. The 483 noted that the informed consent document lacked an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and in the event of a research-related injury to the subject as required by 21 CFR 50. DSI notes that the study was not conducted under an IND and further that the study was conducted only at foreign sites, thus there is no requirement for the study to abide by the requirements of 21 CFR 50.

The EIR for the inspection site has not been received at the time the CIS was written. Information noted above is based on the Form FDA 483 and communications received from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Final classification of this investigation is pending receipt and review of the EIR.

d. Assessment of data integrity: DSI questions the overall integrity of the data at this site because (1) the study drug could not be verified to have been maintained at the proper refrigeration temperature during the study; (2) white out was used for multiple corrections in the medical records; and (3) original source documents used to calculate creatinine clearance levels were not maintained at the site. DSI notes that in the one case that the field investigator calculated the creatinine clearance from source records, the value obtained did not equal that reported on the CRF. In addition, DSI notes that (a) subject #508 did not meet the protocol definition of having resistant disease and should not have been enrolled into the study, (b) subject #502 received post study chemotherapy and thus may not have met the protocol requirement for having resistant disease, and (b) subject # 505's date for the last dose of first line chemotherapy was off by 2 days which could have impacted the total duration of response to prior chemotherapy, thus possibly impacting whether or not the subject was stratified correctly during the study. DSI further notes that the discrepancies noted above for inaccurate reporting of GGT and hypokalemia toxicity may affect the safety profile of the drug for these subjects.

3. Center: 101
Dr. Tudor-Eliade Ciuleanu
"I. Chiricuta" Institute of Oncology
Cluj Napoca, 400015, Romania

a. At this site, 14 subjects were randomized. An audit of 8 randomized subjects was conducted at this site.

b. Limitations of inspection: Records are in foreign language.

c. The following were deviations noted at this site:

i. The investigator did not follow the investigational plan [21 CFR 312.60].

1. The protocol specified that subjects to be included into the study were to have a serum bilirubin test performed. Subject #465 was randomized to the study without having a serum bilirubin test.

2. The protocol specified that on specific study days, subjects randomized to the oral topotecan and active symptom control arm were to receive protocol required CBC/Differential/Platelets and routine chemistries (ie also termed blood chemistries in the protocol). The following subjects did not have these tests done.

   a. For subject #230, only alkaline phosphatase and total bilirubin were obtained on day 15 of cycle one (August 13, 2002) and on day 15 of cycle three (September 25, 2002), CBC/Differential/Platelets and blood chemistries were not performed.

   b. For subject #232 the blood chemistries were not performed on day 15 of cycles one, two, three, & four (October 3, 2002; October 31, 2002; November 28, 2002; & December 23, 2002). In addition the CBC/Differential/Platelets were not done on day 15 of cycle two.

   c. For subject #456 the only routine chemistries performed on day 15 of cycle one was alkaline phosphatase and total bilirubin.

   d. Subject #461's complete routine chemistries were not obtained on (1) day 15 of cycle two (March 11, 2002), (2) day 1 of cycle three or within seven days prior to that day, or (3) day 1 of cycle two or within seven days prior to that day (February 25, 2002).

3. The protocol specified that at the screening visit, a urinalysis was to be performed. Subject #460 did not have a screening urinalysis.

4. The protocol specified that any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study should be recorded on the Medical/Surgical History form within the patient's case report form and exacerbations of preexisting conditions should be reported as adverse events. The CRF for Subject #463 noted that the subject had a grade one asthenia diagnosed in 2001 that was ongoing; however asthenia was again listed as an AE in 2002. It could not be determined if the subject experienced an exacerbation of asthenia during the study for it to be listed as an AE.

5. The protocol specified that within 2 weeks of randomization, a complete medical history including details of malignancy, documentation of histology, prior treatments including response, any residual toxicity related to prior therapies, be performed. Documentation could not be found showing the specific dosing schedule of Cisplatin for Patient #465.

6. The protocol specified that the study medication was to be stored between 2-8°C. There was no documentation of the thermometer used to monitor temperature of the study medication. Per discussions with the field investigator, during the study, the site used an electronic thermometer probe that was placed into the refrigerator. After the study ended, the site threw away that thermometer as they acquired a new one.

ii The investigator did not prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)].

1. There was no documentation available in the research records for Subject #456 to substantiate (a) the subject's reported nausea from May16th to May 20th 2002 and (b) the corresponding concomitant medication of metoclopramide.

2. Discrepancies were noted in the source records and CRF for several subjects:

   a. For subject # 461: (a) The source records showed that there was a partial response to the initial chemotherapy (October 3, 2001); however the CRF shows a complete response, and (b) the source record shows that the subject had a fever of greater than 38°C which would have been a listed as a grade one toxicity; however the CRF noted it as a grade 2.

   b. For subject # 460: (a) the source document calculating creatinine clearance for subject #460 for the date of January 22, 2002 was not found. Using available source records and the formula noted in the protocol, the field investigator calculated the creatinine clearance as 89. However the CRF reported the value as 86; and (b) source records show that the total bilirubin on January 29, 2002 was 2.1mg/dl and the upper limit of normal (ULN) was 1.3mg/dl, thus the subject should have been listed as a grade two bilirubin toxicity. However the CRF reported a grade one toxicity.

   c. For subject #230: (a) Source records show that the subject started on initial therapy treatment for SCLC with etoposide (Vepezid) on October 5, and with Cisplatin on November 6, 2001. However, the CRF indicates that both drugs were started on November 7, 2001; and (b) Source records show the last date that Cisplatin was given to the subject was January 17, 2002, but the CRF shows the last dose as January 18, 2002.

   d. For subject #457: (a) The source show that the subject started on initial therapy treatment for SCLC with Carboplatin on July 10, 2001; However, CRF indicate that Carboplatin was started on July 9, 2001; and (b) the source record show the last date the subject received Carboplatin was on October 4, 2002; however the CRF shows the last dose of Carboplatin on October 3, 2002.

   e. For subject #456: (a) Source records show that the subject received Carboplatin prior to the study; however the CRF reports that the subject received Cisplatin; and (b) Source records show that the subject stopped receiving Cisplatin; (which as noted above should have been Carboplatin) on November 29. 2000; however the CRF reports the drug was stopped on November 30, 2000.

   f. Source records for subject #232, show that that the laboratory value for platelets on December 18, 2002 was 229; however the CRF reports a value of 292.

iii. The 483 noted that the informed consent document lacked whom to contact for answers involving the rights of study subjects as required by 21 CFR 50. DSI notes that the study was not conducted under an IND and further that the study was conducted only at foreign sites, thus there is no requirement for the study to abide by the requirements of 21 CFR 50.

The EIR for the inspection site has not been received at the time the CIS was written. Observations noted above are based on the Form FDA 483 and communications with the investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Final classification of this investigation is pending receipt and review of the EIR.

d. Assessment of data integrity: The majority of the efficacy data generated at this site appear to be acceptable in support of the respective indication. DSI would recommend the review division assess whether the discrepancies noted concerning the drug and/or final dates of the drug given during the first line chemotherapy to treat the subjects # 230, 456, 457, and 465 initial SCLC would have changed the stratification of the subjects during the randomization phase of the study and whether this change could impact the efficacy of the data at this site. In relation to the safety results obtained at this site,

DSI notes that CBC/Differential/Platelets and routine chemistries (blood chemistries) were either (1) not performed for various subjects on specified days throughout the study or (2) discrepant between source and the CRF for many subjects. As these tests and their results were crucial in assessing the safety of the investigational product, DSI recommends that the review division assess whether the discrepancies as a whole could affect the integrity of the safety data at this site.

4. Center: 042
Dr. Mary O'Brien
Royal Marsden Hospital
Department of Medicine
Downs Road
Sutton, Surrey, UK

a. An audit of 7 out of 7 randomized subjects was conducted at this site.

b. Limitations of inspection: None.

c. The following were deviations noted at this site:

i. The investigator did not follow the investigational plan [21 CFR 312.60].

1. The protocol specified that within 2 weeks of randomization or within 7 days of randomization, specific study procedures were to be conducted. Specifically,

a. Subjects #208 and #412 did not receive a neurological assessment within the noted 2 week timeframe.

b. Patients #207, #208, #413, and #415 did not receive the protocol specified urinalysis required within 7 days of randomization.

c. Subject #412 did not have all protocol specified blood chemistries performed prior to randomization.

d. For all subjects enrolled, direct bilirubin was not determined for any patients during either 7 days prior to randomization or as required during any time (i.e. day 8 or 15 for all cycles) during the study.

e. Subject # 413 did not have an ECG done within two weeks prior to randomization.

2. The protocol specified that on specific study days, subjects randomized to the oral topotecan and active symptom control arm were to receive protocol required CBC/Differential/Platelets and routine chemistries (ie also termed blood chemistries in the protocol). The following subjects did not have these tests done.

a. Subjects #207, #208, and #413 randomized to the active treatment arm did not receive the protocol required urinalysis test at all visits during the study .

b. Subject # 207 did not have CBC/Differential/Platelets and/or complete blood chemistries performed either on the 7 days prior to day 1 of cycle 4 or on day 15 of cycle four.

c. ECG's were not completed as required by the protocol. Subject #413 and #208 did not have ECGS completed after the last dose of study medication. Subject #412 received their first ECG on the same day that they received study medication.

d. Subject #208 did not have a complete physical exam on day 1 of cycle six of the study in that the subject did not have their body weight measured.

3. The protocol excluded subjects who had been treated with an investigational drug within 30 days or five half-lives (whichever was longer) prior to entry into the study. Subject # 206, #414, and #415 received an experimental vaccine prior to participating in the study. There was no vaccine half-life information available at the site to determine if the subjects met this exclusion criterion.

4. The protocol specified that the study medication was to be stored between 2-8°C. There were no records to verify that temperature sensors used to document the pharmacy refrigerators were calibrated and also no documentation to indicate which refrigerator in the pharmacy was used for the storage of the study medication.

5. The protocol specified that to be enrolled into the study, subjects were to have relapsed, resistant disease and thus not be candidates for further intravenous chemotherapy. DSI notes that the following subjects did not receive post study intravenous chemotherapy, however did receive post study chemotherapy: #208, 414, 415. Thus these subjects may not have met the protocol definition for having resistant disease.

ii The investigator did not prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)].

1. Discrepancies were noted between the source and the CRF for grading of toxicity in relation to AEs experienced by the subjects or evaluation of reports concerning CBC/Differentials/Platelets or blood chemistries.

a. Subject #412 source document noted a grade 3 myalgia on May 16, 2002. On May 28, 2002 the source showed that the subject myalgia had not changed. However the CRF for the May 28, 2002 visit showed the myalgia was a grade 2.

b. Subject #413 source documents showed that the subject experienced grade 2 nausea from August 29-September 1, 2001. However the CRF shows a grade 1.

c. Subject #207 was noted to have a grade 1 pyrexia on November 21, 2002 per response to a data query. However, source documents showed the subject had a temperature below that required to meet the definition of grade 1.

d. The last dose of initial chemotherapy for 6 of 7 subjects was reported inaccurately on the CRF.

Subject	Source record –date of last dose of chemotherapy	CRF – date of last dose of chemotherapy
#206	February 21, 2002	February 19, 2002
#207	July 12, 2002	July 10, 2002
#208	August 17, 2002	August 15, 2002
#412	November 30, 2001	November 28, 2001
#414	April 26, 2002	April 24, 2002
#415	April 13, 2002	April 11, 2002

e. Subject #414 did not have a microscopic evaluation done of the screening urinalysis when blood was identified.

f. Subject #208 and # 413 source records and CRF were discrepant on several dates with respect to AE reporting

Subject	Date	Source records	CRF
413	August 28, 2001	developed coryzal symptoms prior to August 28, 2001	No mention of AE
413	Aug 7 to 11, 2001	Nothing in source to validate	Experienced Grade 1 fever
413	August 2001 to September 17, 2001	Nothing in source to validate	Experienced Dry Mouth
208	March 2003	Document dated March 21, 2003 noted that the subject had a "four week history of dysequilibrium"	Experienced dizziness starting in March 2003
208	December 1, 2002 vs. January 2003	Subject had dry mouth starting on January 30, 2003.	Subject had dry mouth starting on December 1, 2002

g. A discrepancy was noted as to when subject # 413 screening visit date occurred: CRF reports August 6, 2001, source shows July 30, 2001.

h. The protocol specified that any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study should be recorded on the Medical/Surgical History form within the patient's case report form and exacerbations of preexisting conditions should be reported as adverse events. The CRF for Patient #207 lists grade one tiredness both as an ongoing condition first diagnosed in 2002 and as an adverse event from December 2-9, 2002 and December 23-30, 2002. However source records could not verify that tiredness was considered an exacerbation of the preexisting condition. According to a data query sent to the site the investigator listed tiredness as an AE as she believed there was a suspected relationship to the investigational drug.

iii. The investigator did not prepare or maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]. Specifically the drug disposition could not be verified as the computerized inventory of study medication kept by the pharmacy could not fully provide complete information to cover the date and quantity of drug dispensed to or returned by all subjects during the time of the study.

iv. The 483 notes that the informed consent document lacked an explanation of whom to contact for answers about research subject's rights and in the event of a research-related injury as required by 21 CFR 50. DSI notes that the study was not conducted under an IND and further that the study was conducted only at foreign sites; thus there is no requirement for the study to abide by the requirements of 21 CFR 50.

The EIR for the inspection site has not been received at the time the CIS was written. Observations noted above are based on the Form FDA 483 and communications with the investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Final classification of this investigation is pending receipt and review of the EIR.

d. Assessment of data integrity: DSI questions the integrity of the data at this site. Specifically DSI notes that 3 of 7 subjects received an experimental vaccine prior to participating in the study. It can not be determined what impact the receipt of this experimental vaccine had on the subjects as it could not be determined if the vaccine was given during the exclusionary time period. Also, 3 subjects received post study chemotherapy; thus these subjects may not have met the definition of having resistant disease. It addition, it was noted that for 6 of 7 subjects, the date for the last dose of chemotherapy was off by two days. The protocol specified that randomized subjects were to be stratified based on duration of response to prior chemotherapy. DSI recommends that the review division determine whether the above noted date discrepancies for the last dose of chemotherapy would have placed subjects into a different strata during randomization and thus potentially affect the study outcome. In reference to the safety data at this site, DSI notes that not all CBC/Differentials/Platelets, blood chemistries, urinalysis, EKGs were performed for all subjects as required by the protocol prior to or during the course of the study. As noted above, direct bilirubin was not determined for any subjects at any time during the study. Additionally, discrepancies were noted in the reporting of AEs. Lastly DSI can not confirm that the investigational drug was stored appropriately during the study or was dispensed and/or returned accurately as records from the pharmacy were not accurately maintained or could be produced. Overall, DSI would recommend that the data from this site not be used in support of the respective indication.

5. Center: 092
Prof. Yaroslav V. Shparyk
State Regional Oncology Medical and Diagnostic Centre
Department of Chemotherapy
2A Hashek Street
Lviv, 79031, Ukraine

a. An audit of 8 out of 8 randomized subjects was conducted at this site.

b. Limitations of inspection: Records were in a foreign language.

c. No 483 was issued at the site. The following were deviations noted in communications sent from the FDA field investigator:

i. The investigator did not follow the investigational plan [21 CFR 312.60]. Subjects enrolled into the study were to have resistant disease. Subject #11176, randomized to the ASC arm had withdrawn consent to be in the study but later received IV chemotherapy. The patient expired two weeks later. Per the FDA field investigator, the clinical investigators noted that they believed that post study IV chemotherapy was too harsh for this subject, but the subject and the family insisted on the subject receiving it.

ii. The investigator did not prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)].

1. The field investigator noted that all laboratory samples were sent to a local lab for analysis and reporting. The local laboratory was noted to be outdated and also incapable of analyzing bicarbonate as required by the protocol. The machine used by the laboratory to analyze samples only had the capacity to print out the results of the samples being analyzed and not be able to print out identifying information as to who the sample belonged to. The site in conjunction with the lab created a worksheet whereby the lab technicians would take the information from the printouts and handwrite the corresponding values for various tests onto the worksheets. Once the lab technicians handwrote the test values onto the worksheets, they subsequently threw away

the original laboratory printouts. Thus the field investigator could not verify what was written on the worksheets as accurate records.

The EIR for the inspection site has not been received at the time the CIS was written. Observations noted above are based on communications with the investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. Final classification of this investigation is pending receipt and review of the EIR.

d. Assessment of data integrity: The majority of the efficacy data at this site appear acceptable in support of the respective indication. However, the FDA field investigator noted that all of the subjects randomized to the ASC arm of the study withdrew consent shortly after randomization. As the study examined the overall survival between subjects on the ASC arm versus those on the ACS plus topotecan arm, DSI believes that it would be hard to compare the overall survival of subjects between each group, if all the subjects on the ASC arm withdrew from the study before survival could be determined. In reference to the safety data, DSI notes that the integrity of the safety data obtained at this site could not be verified as the local laboratory threw out all the original printouts relating to laboratory procedures conducted at their site.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted above are based on the Form FDA 483 and/or communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Dan-My T. Chu, PhD
Regulatory Review Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Joseph Salewski,
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dan-My Chu
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Joseph Salewski
9/17/2007 08:29:13 AM
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b(4)

MEETING MINUTES

DATE: February 21, 2006 **TIME:** 3:00PM **LOCATION:** Room 2201

IND/NDA: IND: 42,993 **Meeting Request Submission Date:** December 20, 2005
FDA Response Date: January 09, 2006
Briefing Document Submission Date: January 26, 2006

DRUG: HYCAMTIN (topotecan hydrochloride) Oral

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of MEETING: EOP2

b(4)

Proposed Indication:

FDA PARTICIPANTS:

Robert L. Justice, M.D., Acting Div. Director
Ramzi Dagher, M.D., Acting Div. Deputy Director
Ann Farrell, M.D., Clinical Team Leader *(Meeting Chair)*
Michael Brave, M.D. Clinical Reviewer
Gerald Sokol, M.D. Clinical Reviewer (consult)
Brian Booth, Ph.D., Clinical Pharmacology Team Leader
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer
Mark Rothman, Ph.D., Acting Statistical Team Leader
Yuan Li Shen, Ph.D., Statistical Reviewer
Kim Robertson, Consumer Safety Officer *(Minutes Recorder/Facilitator)*

INDUSTRY PARTICIPANTS:

Gaya Anschuetz, M.S., Principal Statistician
Mark S. Berger, M.D., Director, Medicines Development Center-Clinical Oncology
Debasish Roychowdhury, M.D., Vice President, Medicines Development Center-Clinical Oncology
Richard Swenson, Ph.D., Director, Regulatory Affairs-Oncology
Sesha Reddigari, Ph.D., Lead Scientist, Medicines Development Center-Oncology

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X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Ann Farrell
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MEETING MINUTES

MEETING DATE: Sept. 12, 2002 **TIME:** 9:00 **LOCATION:** C (3004)

IND: 42,993 **Meeting Request Submission Date:** 7-12-02
Briefing Document Submission Date: 8-9-02

DRUG: oral topotecan **INDICATION:** relapsed SCLC

SPONSOR: GlaxoSmith Kline **TYPE of MEETING:** pre-NDA

FDA PARTICIPANTS: Richard Pazdur, M.D., Dir., DODP
Lilia Talarico, M.D., Assoc. Dir., DODP
Steve Hirschfeld, M.D., Medical Officer, DODP
Yung-Ao Hsieh, Ph.D., Chemist, DODP (pre-mtg only)
W. David McGuinn, Ph.D., Pharmacologist, DODP (pre-mtg only)
Atik Rahman, Ph.D., Clin. Pharm/Bioph Team Leader, DODP
Carl-Michael Staschen, Ph.D., Clin. Pharm. Reviewer, DODP
Anne Zajicek, Ph.D., M.D., Clin. Pharm. Reviewer, DODP
Ning Li, Ph.D., Statistician, DODP
Paul Zimmerman for Dotti Pease, Project Manager, DODP
William Gradishar, M.D., ODAC consultant (pre-mtg only)
Tom Simon, patient consultant (pre-meeting only)
JoAnn Minor, OSHI

SPONSOR PARTICIPANTS: GlaxoSmithKline
Kelly Grotzinger, Ph.D., Global Health Outcomes – North America
Jeremey Levin, M.D., Ph.D., Dir., Oncology, Clin. Dev. & Med. Affairs
Alaknanda Preston, Ph.D., Asst. Dir., Biostatistics and Data Sciences
Richard Swenson, Ph.D., Dir., Oncology, Regulatory Affairs
J. Mel Sorensen, M.D., VP, Oncology – MSI, Clin. Dev. & Med. Affairs
Craig Metz, Ph.D., VP, Regulatory Affairs
Ohad Amit, , Ph.D., Assoc. Dir., Biostatistics and Data Sciences
Graham Ross, Clin.
Ruth Poulin, Sr. Scientist, Oncology, Clinical Dev. & Med. Affairs
Paul Wissel, M.D., Group Dir., Oncology Clinical Dev. & Med. Affairs

MEETING OBJECTIVES: Discuss adequacy of proposed NDA and sponsor's specific questions.

BACKGROUND: Oral topotecan is proposed for use in relapsed SCLC. IV topotecan is also approved for use in ovarian cancer. After discussion of sponsor's questions internally, FDA faxed our responses to GSK on September 6, 2002. The meeting was held to clarify FDA responses.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. GSK accepts that FDA cannot comment on the approvability of a file prior to its submission. Nevertheless, GSK would appreciate a discussion of the efficacy/safety results of Studies 065 and 396 with FDA prior to preparation of the dossier.

   FDA – A discussion of efficacy/safety results is a review issue.

2. GSK plans to present pooled adverse event data from Studies 065 and 396 in labeling. If adverse events data in SCLC patients are similar to adverse events data in relapsed ovarian cancer patients, does the Agency agree that the SCLC patients (n=205) and [redacted] data should be combined for labeling? b(4)

   FDA - Yes

3. Will the FDA accept pooling of the efficacy/safety data from Studies 065 and 396 as supportive evidence of the clinical benefit of both oral and intravenous topotecan?

   FDA – No. You may combine safety data, but the efficacy data may either be presented separately or subjected to a Meta analysis. if you choose the latter approach, please discuss further with the Division statisticians.

4. Does the Agency have any comments on the proposed analysis of these efficacy data?

   FDA – See response to #3.

5. Does the Agency have any comments on the proposed analysis of symptom data?

   FDA – You should analyze symptom data separately for each study.

General NDA Format Questions

As a result of the International Conference on Harmonization (ICH), FDA has agreed to accept NDA submissions in Common Technical Document (CTD) format. GSK plans to use the CTD format for this NDA in the **third quarter 2003**. It is anticipated, GSK will have several questions regarding formatting of the NDA in CTD format; these questions will be presented to FDA when the meeting briefing document is submitted. ***(none submitted – Dotti)***

We wish to discuss GSK's plan to provide this submission in Common Technical Document (CTD) format. We would like to specifically discuss the scope and format of the efficacy and safety information within Module 2 (Summaries) of the CTD and linkage between these summaries and more detailed analyses and datasets that will be provided in Module 5 (Clinical Study Reports).

GSK plans to provide this submission electronically as a CTD and plans to follow the existing guidance (August 2001). We would like to review the file structure of the planned submission to insure that it will facilitate access to all documents and data included within the submission.

GSK has prepared a prototype CTD submission to illustrate the aspects of the transition from traditional NDA format to the CTD format. This should give the review team a good indication as to how they will be able to access key efficacy and safety information. We would like to present this prototype to the review team to get their feedback.

FDA – refer to FDA guidances on electronic NDAs and CTD. We will not be able to comment on any proposal presented at the meeting next week if it was not included in the package.

Additional Statistical Comment:

Please provide the Meta analysis presentation to the IND.

Additional Clinical Pharmacology and Biopharmaceutics comments.

1. **Have you studied the dose proportionality of oral topotecan around the therapeutic dose?**

2. **Is the clinical formulation of oral topotecan the same as the to-be-marketed formulation?**

   How do you plan to show the bioequivalence of formulation ——— This will be a fileability issue. Please resolve this issue with the Division before filing this application. b(4)

These issues will be addressed at a separate CMC/biopharmaceutics pre-NDA meeting.

ACTION ITEMS:

1. A pre-NDA meeting will be requested to discuss CMC and clinical pharmacology/ biopharmaceutics issues

2. The NDA is planned for 3rd or 4th quarter of 2003.

Dotti Pease, Project Manager

Steven Hirschfeld, M.D.
Medical Officer

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/s/

Steven Hirschfeld
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MEETING MINUTES

MEETING DATE: November 5, 1998 **TIME:** 10:30am **LOCATION:** Conf. Room G

IND#: 42,993

Meeting Request Submission Date: September 29, 1998
Briefing Document Submission Date: October 13, 1998

DRUG: Oral Hycamtin (topotecan HCl)

SPONSOR/APPLICANT: SmithKline Beecham Pharmaceuticals

TYPE OF MEETING:

1. End-of-Phase 2

2. **Proposed Indication:** For the treatment of patients with small cell lung cancer sensitive disease after the failure of initial chemotherapy.

FDA PARTICIPANTS:

Robert Justice, M.D.	----	Acting Director, Division of Oncology Drug Products
Julie Beitz, M.D.	----	Acting Deputy Director
Grant Williams, M.D.	----	Medical Team Leader
Steven Hirschfeld, M.D., Ph.D.	----	Medical Reviewer
David Smith, Ph.D.	----	Biometrics Reviewer
W. David McGuinn, Ph.D.	----	Pharm./Tox. Reviewer
Atik Rahman, Ph.D.	----	Biopharmaceutics Team Leader
Debra Catterson, R.Ph.	----	Project Manager

FDA PARTICIPANTS (Pre-Meeting Only):

Robert Temple, M.D.	----	Director, Office of Drug Evaluation 1
Rachel Behrman, M.D.	----	Deputy Director, Office of Drug Evaluation 1

INDUSTRY PARTICIPANTS:

David Krause, M.D.	----	Vice Pres., Clinical R&D and Med. Affairs-N. America
Scott Z. Fields, M.D.	----	Group Dir., Clinical R&D and Med. Affairs-N. America
Robert Beckman, M.D.	----	Director, Clinical R&D and Med. Affairs-N. America
David Graden, Ph.D.	----	Assis. Dir., Clinical R&D and Med. Affairs-N. America
Ruth Poulin, R.N.	----	Senior Clinical Associate, Clinical R&D- N. America
David Fitts, M.P.H., Ph.D.	----	Associate Director, Biometrics
Steve Lane, M.S.	----	Senior Statistician, Biometrics
Mike Henry, M.S.	----	Director, Project Management
Diane Mould, Ph.D.	----	Assis. Director, Drug Metab. and Pharmacokinetics
Richard Swenson, Ph.D.	----	Assoc. Director, U.S. Regulatory Affairs
Gregory Christensen	----	Chemist, Pharmaceutical Development
	----	

b(4)

MEETING OBJECTIVE:

SmithKline Beecham Pharmaceuticals requested this End-of-Phase 2 meeting to obtain the Agency's guidance on their development program for the use of Oral Hycamtin in the treatment of patients with small cell lung cancer sensitive disease after the failure of initial chemotherapy. The sponsor would also like to discuss the results of their Oral Hycamtin studies in patients with ——— b(4)

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

SPONSOR'S QUESTION #1:

In patients with small cell lung cancer, results from ——— provide evidence that the efficacy and safety of oral *Hycamtin* are similar to those provided by the intravenous formulation. With the support of data demonstrating the similarity of effect for the oral and intravenous formulations in an ——— could the results of ——— be the basis for approval of *Hycamtin* in the treatment of patients with small cell lung cancer sensitive disease after the failure of initial chemotherapy? b(4)

FDA ANSWER:

- Probably not, because:

  a) Exposure to drug appears to be less with the oral formulation.

  b) The small cell lung cancer study is too small to be reassuring regarding efficacy.

  c) Activity of the oral formulation in the ——— study appears to be inferior to the intravenous formulation. b(4)

  d) The Division recommends a confirmatory randomized controlled trial in sensitive small cell lung cancer comparing the two formulations. The sponsor could consider refining the dose.

SPONSOR'S QUESTION #2:

[redacted] b(4)

FDA ANSWER:

- Probably not, because:

  a)

  b)

  c)

b(4)

ACTION ITEM:

1. The sponsor plans to submit study proposals for both indications to the Agency.

The meeting was concluded at 12:00 noon. There were no unresolved issues or discussion points.

Concurrence Chair: _____

Debra Catterson, R.Ph.
Minutes Preparer

Grant Williams, M.D.
Medical Team Leader

cc: Original IND 42,993
HFD-150/Div File
HFD-150/JBeitz
HFD-150/GWilliams
HFD-150/SHirschfeld
HFD-150/DSmith
HFD-150/WMcGuinn
HFD-150/ARahman
HFD-150/DPease
HFD-150/LVaccari
HFD-150/DCatterson/11.10.98

MEETING MINUTES

TELECONFERENCE MINUTES

MEETING DATE: April 18, 2001 **TIME:** 1:30 p.m. **LOCATION:** WOC2/rm 2064

IND: 42,993

Meeting Request Submission Date: 2-23-01; sn 197 (MR)
Additional Document Dates: 3-20-01; sn 200 (GC)

DRUG: Topotecan hydrochloride – Oral

SPONSOR/APPLICANT: GlaxoSmithKline (formerly SmithKline Beecham Pharmaceuticals)

TYPE of MEETING:

1. End-of-Phase 2
2. **Proposed Indication:**

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products
Donna Griebel, M.D.	--	Clinical Team Leader, Division of Oncology Drug Products
Steven Hirschfeld, M.D., Ph.D.	--	Clinical Reviewer
Rajeshwari Sridhara, Ph.D.	--	Statistical Reviewer
Atiqur Rahman, Ph.D.	--	Clinical Pharmacology and Biopharmaceutics Team Leader
Lydia Kieffer, Pharm. D.	--	Clinical Pharmacology and Biopharmaceutics Reviewer
Dianne Spillman	--	Project Manager

INDUSTRY PARTICIPANTS:

Stephen Lane, M.S.	--	Senior Statistician, Biometrics and Data Sciences
Jeremey Levin, M.D.	--	Oncology, North American Medical Affairs
Ruth Poulin, R.N.	--	Oncology, North American Medical Affairs
Mark Russo, M.D., Ph.D.	--	Clinical Development Therapeutics, Cell Signaling, Biologics Head
Richard Swenson, Ph.D.	--	Associate Director, Regulatory Affairs/Oncology
Paul Wissel, M.D.	--	Head, Clinical Development, Oncology, North America Medical Affairs

b(4)

Consultants: --

BACKGROUND:

1. December 11, 2000 EOP2 meeting:
2. February 23, 2001 *IND submission - serial #197*: EOP2 meeting request
3. March 15, 2001 FDA fax: confirmation of 4-18-01 meeting date
4. March 20, 2001 *IND submission - serial #200*: Meeting package
5. April 17, 2001 FDA fax: Division bullets for 4-18-01 meeting

MEETING OBJECTIVE (from meeting request):

To gain agreement with FDA that the phase 3 clinical development program for oral topotecan will, if successfully executed, obtain FDA approval for this formulation in

11 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Dianne Spillman
5/22/01 01:04:50 PM

Steven Hirschfeld
5/28/01 07:14:03 PM