

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, November 22, 2006 3:34 PM
To: 'Rich.Swenson@gsk.com'
Subject: RE: NDA 22-059 Statistical Query

Thanks Richard. I will forward this to our stat folks and see if there is anything further they will require. Have a wonderful holiday.....I'm logging off as I type.

Kim

Kim J. Robertson
Food and Drug Administration
Consumer Safety Officer
Division of Drug Oncology Products
(301) 796-1441
(301) 796-9845 (fax)
kim.robertson@fda.hhs.gov

From: Rich.Swenson@gsk.com [mailto:Rich.Swenson@gsk.com]
Sent: Wednesday, November 22, 2006 3:29 PM
To: Robertson, Kim
Subject: Fw: NDA 22-059 Statistical Query

Dear Kim:

In response to your recent request, I have our initial responses.

1) Study Report Programs for Study EGF100151

GSK Response: GSK has provided Data Definition Tables which have description and specification of all derived variables. The SAS programs are not "stand alone", and the settings are such that the programs run on our GSK systems. There are many macros that are GSK system dependent, for example format libraries, GSK Drug dictionary for coding concomitant medications. It would take considerable effort and time to make the code work on the FDA systems. Nevertheless, GSK would be happy to discuss this matter further with the Statistician to see how we can accommodate the request.

2) All CRF data listing for study EGF100151

GSK Response: All the CRF data for EGF100151 are contained in the NDA folder 22059 / crt / datasets / egf100151

As usual, this response will be submitted to NDA 22-059. Please let me know if you need additional information.

Regards,

3/12/2007

rich

Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

----- Forwarded by Rich Swenson-7/SB-OTHER/PHRD/SB_PLC on 11/22/2006 03:13 PM -----

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

To Rich.Swenson@gsk.com

22-Nov-2006 12:16

cc

Subject NDA 22-059 Statistical Query

Hello Richard:

I have the following question from our statistical reviewer for your NDA 22-059:

Has GSK included the study report programs and all CRF data listing for study EGF100151 as part of the NDA submission?

The stat reviewer mentioned that she's looking for this, but was unable to locate it.

Thanks Richard,

Kim

Kim J. Robertson

Food and Drug Administration

Consumer Safety Officer

Division of Drug Oncology Products

(301) 796-1441

(301) 796-9845 (fax)

kim.robertson@fda.hhs.gov

Robertson, Kim

From: Rich.Swenson@gsk.com
Sent: Tuesday, November 21, 2006 12:31 PM
To: Robertson, Kim
Subject: Re: FW: NDA 22-059 Tykerb
Attachments: U14572_39_3 CofA (NDA).pdf; Tykerb Impurity Justification Correcter — doc; emfinfo.txt

Dear Kim:

Please note there was an error in our response of 17 November 2006 (incorrect impurity content in the table labeled "Table 1: Impurity Support" submitted as an attachment (Tykerb Impurity Justification V2) on 17 November 2006 in response to your question that day.

The values for the — impurity in "Study RD1999/02391/00 (14-Day Oral Gavage Toxicity Study in Wistar Han Rats) were incorrect with regard to the "Impurity Content"; instead of the — we listed, it should read —. Because of this change, two other values in the attached table also changed (all changed values have a triple asterisks [***]). We apologize for this error and have corrected it in the following attachment.

Also, please note the attached Certificate of Analysis for batch U14572/39/3 (the Certificate of Analysis for batch R5361/143/1 was submitted in response to a previous FDA request of 15 November 2006).

Please call if you have a question or comment. This response will be submitted to NDA 22-059.

Regards,

rich

Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

3/12/2007

FDA Question: Please direct us to the toxicology study(ies) in the NDA where the levels of the following impurities of your drug substance have been qualified at the proposed levels of acceptance. If the Certificate of Analyses for the study(ies) are not included in the NDA, please forward them to us ASAP.

NGT
NGT
NGT
NGT
NGT
NGT

GlaxoSmithKline Response:

The proposed levels of acceptance for the _____ impurities listed above were supported by data from repeat dose toxicity studies where rats, at tolerated doses, were exposed to greater amounts of the impurity than will result when patients receive 1250 mg Tykerb containing the impurities at the levels specified. This data is summarized in the following table. In addition, batch analysis tables identifying levels of _____ impurities for all drug substance batches used in nonclinical toxicology studies are contained in section M.3.2.S.4.4 of the NDA.

In reference to the _____ impurities / _____), the levels specified are in accordance with ICH Q3A and compendial (USP, EP, BP, JP) requirements limiting _____

F

3 Page(s) Withheld

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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED: October 2, 2006	DESIRED COMPLETION DATE: November 10, 2006	OSE REVIEW #: 2006-480
DATE OF DOCUMENT: September 15, 2006	PDUFA DATE: March 15, 2007	

TO: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Tykerb (Lapatinib Tablets) 250 mg	SPONSOR: GlaxoSmithKline
NDA#: 22-059	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Tykerb from a safety perspective. This is considered a final decision. However, if the approval of this NDA is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. We recommend consulting Guirag Poochikian, Chair of the CDER Labeling and Nomenclature Committee for the proper designation of the established name.
4. DDMAC finds the proprietary names Tykerb 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. If you have further questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: October 20, 2006

NDA #: 22-059

NAME OF DRUG: Tykerb
(Lapatinib Tablets)
250 mg

NDA SPONSOR: GlaxoSmithKline

I. INTRODUCTION

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150) for a re-review of the proprietary name "Tykerb", regarding potential name confusion with other proprietary or established drug names. DMETS previously reviewed this name in June 2005 (OSE#05-0160), when the name "Tykerb" was found acceptable from a safety perspective. Insert labeling and containers labels were provided for review and comment from a medication error perspective.

PRODUCT INFORMATION

Tykerb contains lapatinib in a tablet form for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

Tykerb should be used in combination with Xeloda (capecitabine). The recommended dose is 1250 mg once daily (5 tablets daily) in combination with 2000 mg/m²/day of capecitabine days one through fourteen of a 21-day cycle. Tykerb should be taken at least one hour before and one hour after meals. Treatment should be continued until disease progression or unacceptable toxicity occurs. Tykerb is available as 250 mg tablets that are orange film-coated.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Tykerb to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

Office's Text and Image Database was also conducted⁵. The SAEGIS⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Tykerb. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Tykerb acceptable from a promotional perspective.
2. Since the completion of our initial review, the Expert Panel identified six additional proprietary names (Nysert, Tyzine, Keftab, Lyrica, Tygacil, and Ticlid) as having the potential for confusion with Tykerb. Independent investigation identified an additional seven proprietary names (Cycin, K-tab, Tycolet, Triphed, Cytomel, Tysabri, and Tyklid) as having the potential for confusion with Tykerb. These products along with the available dosage forms and usual dosage are listed in Table 1 (see below and pages 4). Eleven of these names will not be reviewed further due to weak orthographic similarities, lack of availability in the marketplace, specialty of use, and/or lack of overlapping products characteristics such as strength, dosage form, and/or directions for use: Cycin, Nysert, Tyzine, Keftab, Lyrica, Tygacil, K-tab, Tycolet, Triphed, Tysabri, and Tyklid. The last drug product "Tyklid" is a ticlipidine product marketed in India. Although the products of Tyklid and Tykerb share look- alike and sound-alike characteristics and an overlapping strength, DMETS believes the actual possibility for confusion with this product and Tykerb to be minimal due to the area of marketing.

Table 1: Potential Look-Alike and Sound-Alike Names Identified for Tykerb

Product Name	Established name, Dosage form(s)	Usual adult dose	Other
Tykerb	Lapatinib Tablets, 250 mg	1250 mg daily	
Ticlid	Ticlipidine Hydrochloride Tablets, 250 mg	1 tablet twice daily.	SA
Cycin (discontinued)	Medroxyprogesterone Tablets, 2.5 mg, 5 mg, and 10 mg	5 to 10 mg daily for 5 to 10 days, beginning day 16 or 21 of the menstrual cycle. For endometrial hyperplasia: Five or 10 mg daily for 12 to 14 consecutive days per month, beginning on day 1 or 16 of the cycle. Secondary amenorrhea: 5 or 10 mg daily for 5 to 10 days.	LA
Keftab (Discontinued)	Cephalexin Hydrochloride Tablets, 250 mg, 333 mg, and 500 mg	One to four grams per day in divided doses.	LA
K-tab	Potassium Chloride Extended-release Tablets, 10 mEq	Prevention: 16 to 24 mEq daily. Treatment: 40 mEq to 100 mEq daily.	LA

⁵ www location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose	Other
Tykerb	Erlotinib Tablets, 250 mg	1250 mg daily	
Tycolet (discontinued)	Hydrocodone Bitartrate and Acetaminophen Tablets, 5 mg/500 mg	One to two tablets every 4 to 6 hours as needed for pain.	LA
Tyzine	Tetrahydrozoline Hydrochloride Nasal Solution 0.05% (15 mL) and 0.1% (30 mL) Nasal Spray 0.1% (15 mL)	Adults and children 6 years and over: 2 to 4 drops or 3 to 4 sprays in each nostril as needed, never more often than every 3 hours. Children 2 to 6 years of age: Pediatric nasal drops 0.05%: 2 to 3 drops be instilled in each nostril as needed, and never more often than every 3 hours.	LA
Lyrica	Pregabalin Capsules, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg	75 mg twice daily to 100 mg three times daily.	LA
Tyagcil	Tigecycline Injection (infusion) 50 mg/vial	100 mg initially, then 50 mg every 12 hours.	LA
Nysert (discontinued)	Nystatin Vaginal Suppository 100,000 Units	One vaginally daily.	LA
Triphed (discontinued)	Tripolidine Hydrochloride/Pseudoephedrine Hydrochloride 2.5 mg/60 mg	Adults: One every 4 to 6 hours. Children: ½ every 4 to 6 hours.	LA
Cytomel	Liothyronine Sodium Tablets, 5 mcg, 25 mcg, and 50 mcg	2 to 100 mcg daily depending on indication.	LA
Tysabri	Natalizumab Injection (Single Use Vial), 300 mg	300 mg infusion every 4 weeks.	LA
Tyklid (India)	Ticlipidine Hydrochloride Tablets, 250 mg	1 tablet twice daily.	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike)/SA (sound-alike).			

B. SAFETY EVALUATOR RISK ASSESSMENT

After a review of the online abbreviation search engine Pharma-lexicon⁷, DMETS notes the name Tykerb is composed of the two medical abbreviations “Tyk” (tyrosine kinase) and “erb” (erbB1, estrogen receptor type B1-tyrosine kinase family). Thus, the name specifies the specific tumor to be treated.

In reviewing the proprietary name of Tykerb, the additional names of concern are Ticlid and Cytomel.

1. Ticlid was identified as a name with similar sound to Tykerb when spoken. Ticlid contains ticlipidine hydrochloride in a 250 mg tablet dosage form, which is used to reduce the risk of thrombotic stroke in patients who have experienced stroke precursors or have had a completed thrombotic stroke. In addition, it is used as an adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation. The recommended dose is 250 mg twice daily with food.

The phonetic similarities stem from the shared two syllable count and leading “T” with the potential for the ensuing long “T” sound. However, Ticlid may be pronounced with a short “T”

⁷ <<http://www.pharma-lexicon.com/>> (14 Nov 2006).

sound that would differentiate the names in speech. In addition, the concluding syllables are distinct in pronunciation with "lid" for Ticlid and "kerb" of Tykerb. These syllables should serve to differentiate the names in speech.

The two drug products share a similar route of administration (oral), dosage form (tablet), and strength (250 mg). However, they differ in indication of use (reduce risk of thrombotic events compared to treatment of advanced or metastatic breast cancer), frequency of dosing (twice daily compared to daily), and duration of therapy (maintenance therapy compared to 14 day cycles). Furthermore, the products differ in dose (250 mg compared to 1250 mg). Due to the differentiating concluding syllables, frequency of dosing, and duration of therapy, DMETS believes the possibility for confusion to be minimal.

2. Cytomel was identified as a name with similar appearance to Tykerb when scripted. Cytomel contains liothyronine sodium in a tablet of 5 mcg, 25 mcg, and 50 mcg as replacement/supplemental therapy in patients with hypothyroidism. In addition, Cytomel may be used as pituitary thyroid-stimulating hormone suppressant and as a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy. The dosage varies in reference to indication and patient response. The doses range from 5 mcg to 100 mcg daily, with incremental increases to therapeutic effect every one to two weeks.

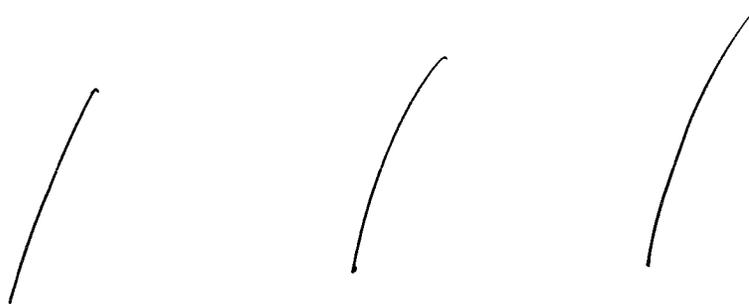
The orthographic similarities stem from the possibility for a scripted lower case "t" to resemble an uppercase "C", followed by the shared "y" and upstroke (of the "t" in Cytomel and "k" of Tykerb). However, the remaining letters ("omel" compared to "erb") may serve to differentiate the names upon scripting.



The image shows two lines of handwritten cursive script. The top line is 'Tykerb' and the bottom line is 'Cytomel'. The 't' in 'Tykerb' and the 'C' in 'Cytomel' are written in a similar style, with a shared 'y' and upstroke that could lead to confusion when scripted.

The drug products overlap in route of administration (oral), dosing frequency, and dosage form (tablet). In addition, the products share similar numerals in the strength (25 mcg compared to 250 mg). However, the products differ in dose (5 mcg to 100 mcg compared to 1250 mg). In light of the differentiating scripting characteristics, differing doses, and lack of direct overlap in strength, DMETS believes the possibility for confusion to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES



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 Deliberative Process

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

/s/

Kimberly Culley-Pedersen
11/17/2006 12:11:19 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
11/17/2006 12:27:22 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/17/2006 01:30:19 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence

Robertson, Kim

From: Rich.Swenson@gsk.com
Sent: Friday, November 17, 2006 5:00 PM
To: Robertson, Kim
Subject: Re: NDA 22-059 Tykerb
Attachments: Tykerb Impurity Justification V2.doc; emfinfo.txt

Dear Kim:

In response to your question today regarding qualification of impurities, please refer to the attached response from our Path/Tox representative.

The 14-Day Oral Gavage Toxicity Study in Wistar Han Rats is presented in NDA 22-059 Module 4.2.3.2.4.

The 26 Week Oral Gavage Toxicity Study in Wistar Han Rats is presented in NDA 22-059 Module 4.2.3.2.6.

The Certificates of Analysis will be forwarded soon.

Regards,

rich

Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

3/12/2007

FDA Question: "Please direct us to the toxicology study(ies) in the NDA where the levels of the following impurities of your drug substance have been qualified at the proposed levels of acceptance. If the Certificate of Analyses for the study(ies) are not included in the NDA, please forward them to us ASAP.

NGT
NGT
NGT
NGT
NGT
NGT

GlaxoSmithKline Response:

The proposed levels of acceptance for the _____ impurities listed above were supported by data from repeat dose toxicity studies where rats, at tolerated doses, were exposed to greater amounts of the impurity than will result when patients receive 1250 mg Tykerb containing the impurities at the levels specified. This data is summarized in the following table. In addition, batch analysis tables identifying levels of _____ impurities for all drug substance batches used in nonclinical toxicology studies are contained in section M.3.2.S.4.4 of the NDA.

In reference to the _____ impurities _____), the levels specified are in accordance with ICH Q3A and compendial (USP, EP, BP, JP) requirements _____

#

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 Deliberative Process

Robertson, Kim

From: Robertson, Kim
Sent: Friday, November 17, 2006 12:01 PM
To: 'Rich.Swenson@gsk.com'
Subject: NDA 22-059 Tykerb

Importance: High

Hello Richard:

Please see the following P/T request with regard to your NDA 22-059. Please submit this information as soon as possible, and please remember to officially submit this to your NDA as well.

Thank you,
Kimmie

Please direct us to the toxicology study(ies) in the NDA where the levels of the following impurities of your drug substance have been qualified at the proposed levels of acceptance. If the Certificate of Analyses for the study(ies) are not included in the NDA, please forward them to us ASAP.

	NGT
	NGT
	NGT
	NG
	NGT
	NGT

Kim J. Robertson
Food and Drug Administration
Consumer Safety Officer
Division of Drug Oncology Products
(301) 796-1441
(301) 796-9845 (fax)
kim.robertson@fda.hhs.gov

Robertson, Kim

From: Rich.Swenson@gsk.com
Sent: Thursday, November 09, 2006 11:42 AM
To: Robertson, Kim
Subject: Fw: NDA 22-059 Tykerb Statistical Questions
Attachments: emfinfo.txt

Dear Kim:

The following is the GSK answer from our statistical scientists. We are still working on your question from the Biopharm Reviewer (i.e., "% treated days during treatment period" for capecitabine given in Study EGF100151).

I shall submit this and all responses to NDA 22-059.

Thanks and Regards,

rich

Richard Swenson, Ph.D.
 Senior Director, US Regulatory Affairs

For Study EGF 100151,

- Is there a difference between the data sets submitted on August 25 and September 13 of 2006?

No. The datasets submitted on August 25 were validated datasets with the November 15, 2005 clinical cut-off. They were resubmitted on Sep 13 along with the complete package

- How would one identify the data used for IDMC interim analysis?

Datasets specifically used to generate data for the IDMC have not been provided to the FDA. The interim analyses that the IDMC reviewed was based November 15, 2005 clinical cut-off. Following the IDMC's recommendation to halt enrollment, GSK initiated a final comprehensive data cleaning effort including a close review of all efficacy and safety data and generation and resolution of data queries to ensure all relevant data up to Nov 15 were available for purposes of a regulatory submission. The submission was based on this validated Nov 15, 2005 data and it is this data that was submitted to the FDA. As a result of these data cleaning efforts, seven additional progression events were noted. In addition to these 7 events, the data clarification process resulted in the inclusion of 3 additional subjects who were randomized prior to 15 Nov, but for whom CRFs were not available for data entry until after the IDMC data were prepared.

----- Forwarded by Rich Swenson-7/SB-OTHER/PHRD/SB_PLC on 11/09/2006 11:24 AM -----

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

To Rich.Swenson@gsk.com

cc

08-Nov-2006 17:16

Subject NDA 22-059 Tykerb Statistical Questions

3/12/2007

Hello Again Richard:

Here are two (2) additional questions our Statistical Reviewers had with regard to NDA 22-059. Please review and submit your responses as soon as possible. Also, please remember to submit your responses to the NDA as well.

For Study EGF 100151,

- Is there a difference between the data sets submitted on August 25 and September 13 of 2006?
- How would one identify the data used for IDMC interim analysis?

Thank you,

Kim

Kim J. Robertson

Food and Drug Administration

Consumer Safety Officer

Division of Drug Oncology Products

(301) 796-1441

(301) 796-9845 (fax)

kim.robertson@fda.hhs.gov

3/12/2007

Robertson, Kim

From: Rich.Swenson@gsk.com
Sent: Wednesday, November 08, 2006 12:25 PM
To: Ryan, Qin
Cc: Ibrahim, Amna; Robertson, Kim
Subject: NDA 22-059: Response to FDA question of 6Nov06
Attachments: emfinfo.txt

Dear Qin:

Attached are the GSK responses to your questions of 6 November 2006. Please let me know if you have additional questions.

Regards,

rich

Richard Swenson, Ph.D.
 Senior Director, US Regulatory Affairs

FDA Questions in bold italics (6Nov06)

1. 16 patients who received treatment that was not assigned for (Study EGF100151 study report Figure 1)

GSK Response: There were 7 patients assigned to the combination and 9 assigned to monotherapy capecitabine (see attached table)

2. Two subjects had study medication discontinued due to a lack of clinical benefit (Study EGF100151 study report Table 3).

GSK Response: We believe you refer to Table 4 (footnote #2). If that is correct, then here are the two patients (both in lapatinib/capecitabine group):

<u>Investigator/subject</u>	<u>reason discontinued medication</u>
043965/487	lack of clinical benefit
060439/1361	lack of clinical benefit

3. Three subjects had study medication discontinued at the investigator's discretion, and one subject due to the study sponsor withdrawing the medication as a result of a dosing error (Study EGF100151 study report Table 3).

GSK Response: We believe you are referring to Table 4 (footnote #3). If that is correct, then the following are the patient ID numbers:

3/12/2007

In the Capecitabine Group

<u>Investigator/Subject</u>	<u>reason discontinued medication</u>
044034/57	Investigator discretion
057790/796	Investigator discretion
015295/203	Investigator discretion (verbatim text: is Investigator attempt to try different therapeutic approach)
033602/480	Dosing error

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, November 08, 2006 10:19 AM
To: 'Rich.Swenson@gsk.com'
Subject: NDA 22-059 Tykerb

Importance: High

Good Morning Richard:

I have an additional Clinpharm request for information for you with regard to your NDA 22-059:

- Table 8.1 on page 1106 of the study report for Study EGF100151 (UM2004/00001/00 EGF100151) includes data on “% treated days during treatment period” for lapatinib. Similar information for capecitabine is not provided in Table 8.2. Would you please provide this information for capecitabine dosing in both treatment arms?

Please provide this information as soon as possible, and please remember to submit this information officially to your NDA as well.

Thanks,
Kim

Kim J. Robertson
Food and Drug Administration
Consumer Safety Officer
Division of Drug Oncology Products
(301) 796-1441
(301) 796-9845 (fax)
kim.robertson@fda.hhs.gov

MEMORANDUM OF TELECON

DATE: November 6, 2006

APPLICATION NUMBER: NDA 22-059, Tykerb (lapatanib ditosylate) Tablets

BETWEEN:

Name: Giselle Limentani, Director of Product Development
Sherry Watson, Director, Global CMC Regulatory Affairs

Representing: GSK

AND

Office of New Drug Quality Assessment

Chi-wan Chen, Deputy Director

Craig Bertha, Chemist, Division of Pre-Marketing Assessment I

Ziao Hong Chen, Chemist, Division of Pre-Marketing Assessment I

Terry Ocheltree, Chemist, Division of Manufacturing Science

Amy Bertha, Regulatory Health Project Manager

Representing: FDA

SUBJECT: Discuss question 4 of the second set of questions of the IR letter dated October 25, 2006.

NDA 22-059, Tykerb (lapatanib ditosylate) Tablets, is for the treatment of patients with refractory advance or metastaic breast cancer and was submitted on September 13, 2006. The PDUFA user fee date is March 13, 2007. This NDA is part of the CMC pilot program. On November 3, 2006, GSK requested a telephone conference in order for FDA to further clarify question 4 of the second set of questions in the IR letter dated October 25, 2006. Below are the question and a summary of the teleconference discussion.

FDA Question 4 from IR letter dated October 25, 2006: Revise the drug product specification such that the level of the genotoxic degradant/impurity — is routinely determined and controlled at release. With reference to the discussion at the 16-JUN-2006, meeting, the data presented in the application clearly indicate that the drug substance does degrade in the formulation and under the specified storage conditions proposed in the new drug application with respect to the formation of the — impurity. We acknowledge that you have presented data indicating that the levels of — do not increase as a result of drug product manufacture. Alternatively, you may propose retesting of the drug substance for the — level immediately prior to use for drug product manufacture.

Meeting Discussion:

GSK asked FDA to further clarify why impurity _____ should be tested at drug product release. FDA explained that reduced testing of degradation products at drug product release is justified according to ICH Q6A for all impurities except _____ is present in the drug substance, and its level was found to increase over time. More importantly, this impurity is genotoxic. FDA asked GSK if they had considered the possibility that the level of this impurity could increase during the storage of the drug substance. GSK explained that they have controls in place and do not see the value of doing an additional test. FDA replied that GSK can provide in their response to the IR letter a proposal to ensure that the impurity level of _____ is controlled. Included in GSK's response to this question should be a justification for why, in this case, ICH Q6A guideline does not apply.

{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager

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

/s/

Amy Bertha
11/29/2006 03:03:34 PM
PROJECT MANAGER FOR QUALITY



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-059

GlaxoSmithKline
2301 Renaissance Boulevard
RN0210 P.O. Box 61540
King of Prussia, PA 19406-2772, USA

Attention: Richard Swenson, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Swenson:

Please refer to your August 25, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tykerb® (lapatinib ditosylate) Tablets, 250mg., received August 25, 2006. We also refer to your submission dated September 15, 2006, received September 14, 2006; the final portion of your Rolling Review submission.

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

1. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

2. Cross referencing is incorrect throughout the labeling.
3. Subheading 8.6 of the Full Prescribing Information: Contents refers to an incorrect reference.
4. Please remove the dashes for dosage strengths.
5. Please refer to “ — ” as “Adverse Reactions” throughout the label.
6. Please remove “ — ” 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

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

/s/

Ramzi Dagher

11/24/2006 08:41:17 AM

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

CLINICAL INSPECTION SUMMARY

DATE: November 15, 2006

TO: Kim J. Robertson, Regulatory Project Manager
Qin Ryan, M.D., Clinical Reviewer
Division of Oncology Drug Products, HFD-150

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Lauren Iacono-Connors, Ph.D.
Reviewer, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of all EIRs

NDA: 22059/000

NME: Yes

APPLICANT: GlaxoSmithKline

DRUG: Tykerb® (Lapatinib ditosylate; GW572016)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Lapatinib in combination with capecitabine for the treatment of women with refractory advanced or metastatic breast cancer who have ErbB2 over expression and who have received prior therapy which included anthracyclines, taxanes, and trastuzumab.

CONSULTATION REQUEST DATE: September 15, 2006

DIVISION ACTION GOAL DATE: December 15, 2006

PDUFA DATE: March 13, 2007

I. BACKGROUND:**Drug Product:**

Tykerb® (Lapatinib ditosylate; GW572016) is an orally administered small molecule reversible tyrosine kinase inhibitor that targets both ErbB1 and ErbB2 receptors. The overexpression of ErbB1 and ErbB2 has been associated with poor prognosis and reduced overall survival in

patients with a variety of cancers. Overexpression of ErbB2 is detected in ~30% of human breast cancers and those cancers have been reported to be more aggressive than ErbB2 negative cancers. Trastuzumab, a monoclonal antibody directed against ErbB2, is approved in combination with other antineoplastic agents for use against ErbB2 positive metastatic breast cancers and has been demonstrated to provide clinical benefit in ErbB2 positive cancers. The sponsor seeks approval of Tykerb® in combination with capecitabine for the treatment of women with refractory advanced or metastatic breast cancer who have ErbB2 over expression.

This drug is a new molecular entity and is purported by the sponsor to provide a critical treatment option for women with refractory advanced or metastatic breast cancer.

One phase III study has been identified by the review division for audit. The study, EGF100151, was carried out at 128 centers in 19 countries. For the study period between March 29, 2004 and November 15, 2005 (interim analysis cut-off date) a total of 324 subjects were randomized to Lapatinib + capecitabine (163 subjects) or capecitabine (161 subjects). A prespecified interim analysis was planned after 133 investigator reported events of progression or deaths due to breast cancer. The primary endpoint was time to tumor progression as determined by an independent radiological review committee (IRC) blinded to treatment arms. The interim analysis found evidence to suggest superior efficacy for Lapatinib plus capecitabine, justifying early reporting of study results based on protocol-specified criteria. On March 20, 2006 the IRC unanimously recommended that the study sponsor halt further enrollment.

Study EGF100151 was a multicenter, non-blinded, phase III study comparing 2 therapy regimens for the treatment of metastatic breast cancer in women. EGF100151 had an originally planned enrollment target of 528 subjects. At the time recruitment was halted (April 3, 2006) a total of 399 subjects were randomized. The protocol was then amended to allow subjects in the monotherapy control group to transfer to the active study arm; Lapatinib plus capecitabine treatment, if seen as appropriate by both the subject and the treating clinician.

The phase III protocol and its execution by Sandra Franco, M.D., Memorial Regional Cancer Institute in Hollywood, Florida, Mamta Kalidas, M.D., Baylor College of Medicine Breast Care Center in Houston, Texas, Stephen Chan, M.D., Nottingham City Hospital, Department of Clinical Oncology, Nottingham, UK, and Agnieszka Jagiello-Gruszfeld, M.D., of the Mazurskim Centrum Onkologii, Olsztyn, Poland participated as primary investigators on the protocol audited. Four subjects were randomized at each of sites #92434 and #90960, the Memorial Regional Cancer Institute in Hollywood, Florida, and the Baylor College of Medicine Breast Care Center in Houston, Texas, respectively. Thirteen subjects were randomized at site 91482, Nottingham City Hospital, Department of Clinical Oncology, Nottingham, UK, and 11 subjects were randomized at site 91450, Mazurskim Centrum Onkologii, Olsztyn, Poland. In addition, inspections of both the sponsor and one contract research organization was conducted on the listed study performed by the investigators mentioned above, completing the sponsor and monitor compliance program (CP 7348.810).

II. RESULTS:

Inspected Entity	City, State\Country	Protocol	Inspection Dates	EIR Received Date	Final Classification
Sandra Franco, M.D.	Hollywood, Florida	EGF100151	October 6-13, 2006	Pending FLA-DO	Pending
Mamta Kalidas, M.D.	Houston, Texas	EGF100151	TBD	Pending DAL-DO	Pending
Stephen Chan, M.D.	Nottingham, UK	EGF100151	TBD	Pending FLA-DO	Pending
Agnieszka Jagiello-Gruszfeld, M.D.	Olsztyn, Poland	EGF100151	TBD	Pending FLA-DO	Pending
GlaxoSmithKline	King of Prussia, PA	EGF100151	TBD	Pending PHI-DO	Pending
/	/	EGF100151	TBD	Pending	Pending

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) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

1. **Sandra Franco, M.D.**
 Memorial Regional Cancer Institute
 Memorial Breast Cancer Center
 3700 Johnson Street
 Hollywood, Florida 33021

Protocol Number	Subjects Randomized	Subjects Audited
EGF100151	4	4

a. What was inspected?

The study records of 4 subjects for study EGF100151 were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid to consistency of efficacy endpoint achievement source documents found at the site with that submitted to the agency in support of the NDA. The FDA investigator also assessed the date and cause of death, and any SAEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

The clinical investigator was generally found to be adequate in the execution of the studies identified for audit. The studies were found to be well controlled and well documented. However, several regulatory deviations were observed. Consistent with the routine clinical investigator compliance

program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. AEs and SAEs were properly documented and reported to the sponsor and to the IRB in a timely manner. A Form FDA 483 was issued citing 2 observations.

Observation 1. The investigation was not conducted in accordance with the investigational plan. Specifically, Subjects 761 and 762 did not have the weekly assessment for the first two weeks of the study (hemoglobin, hematocrit, red blood cell count, white-blood cell count with differential and platelet count); hematology test. There is no documentation of waiver from the sponsor as to acceptance of the deviation for continuing the study subjects in the study.

Observation 2. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests. Specifically, a new version of the informed consent dated June 25, 2005 was approved by the IRB on 8/8/05. The version incorporated the risk of neutropenia. Subject 759 signed this version on 04/12/06. She was taken off the study on 10/19/05.

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

d. Assessment of data integrity: The data from Dr. Franco's site, associated with protocol EGF100151, submitted to the agency in support of NDA 22059, appear reliable based on available information.

2. **Mamta Kalidas, M.D.**
Baylor College of Medicine
Breast Care Center
6550 Fannin Street
Suite 701
Houston, Texas 77030

Protocol Number	Subjects Randomized	Subjects Audited
EGF100151	4	4

a. What was inspected?

The study records of 4 subjects for study EGF100151 were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid consistency of efficacy endpoint achievement source documents found at the site with that submitted to the agency in support of the NDA. The FDA investigator also assessed the date and cause of death, and any SAEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary

The investigator was found to be adequate in the execution of the study. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data

found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. No deviations were observed. AEs and SAEs were properly documented and were sent to the sponsor and to the IRB in a timely manner. There was no evidence to suggest that the sponsor had influenced the site in reaching conclusions regarding treatment results. No Form FDA 483 was issued.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on preliminary communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Kalidas' site, associated with protocol EGF100151, submitted to the agency in support of NDA 22059, appear reliable based on available information.

3. **Stephen Chan, M.D.**
Nottingham City Hospital
Department of Clinical Oncology
Next to Fraser Ward
H Block 1st Floor
Hucknall Road
Nottingham
NG5 1PB
UK

Protocol Number	Subjects Randomized	Subjects Audited
EGF100151	13	13

a. What was inspected? The study records of 13 subjects for study EGF100151 were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid consistency of efficacy endpoint achievement source documents found at the site with that submitted to the agency in support of the NDA. The FDA investigator also assessed the date and cause of death, and any SAEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

The investigator was found to be adequate in the execution of the study. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. Documentation and reporting of AEs and SAEs were assessed. There was no evidence to suggest that the sponsor had influenced the site in reaching conclusions regarding treatment results. No Form FDA 483 was issued

The EIR is currently being finalized by the FDA investigator and will be submitted to DSI upon completion. The observations noted above are based on preliminary communications from the field

investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Chan's site, associated with protocol EGF100151, appear reliable based on available information.

4. **Agnieszka Jagiello-Gruszfeld, M.D.**
ZOZ MSWiA z Warminsko
Mazurskim Centrum Onkologii
Oddzial Chemioterapii – Chemotherapy Department
Ul. Wojska Polskiego 37
10-228 Olsztyn, Poland

Protocol Number	Subjects Randomized	Subjects Audited
EGF100151	11	11

a. What was inspected? The study records of 11 subjects for study EGF100151 were audited in accordance with the clinical investigator compliance program, CP 7348.811. For these audited subjects the record audit included comparison of source documentation to CRFs with particular attention paid consistency of efficacy endpoint achievement source documents found at the site with that submitted to the agency in support of the NDA. The FDA investigator also assessed the date and cause of death, and any SAEs and informed consent forms.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

The investigator was found to be adequate in the execution of the study. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. Documentation and reporting of AEs and SAEs were assessed. There was no evidence to suggest that the sponsor had influenced the site in reaching conclusions regarding treatment results. No Form FDA 483 was issued.

The EIR is currently being finalized by the FDA investigator and will be submitted to DSI upon completion. The observations noted above are based on preliminary communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data from Dr. Jagiello-Gruszfeld's site, associated with protocol EGF100151, appear reliable based on available information.

5. **GlaxoSmithKline**
Senior Director, US Regulatory Affairs
2301 Renaissance Boulevard
P.O. Box 61540
King of Prussia, Pennsylvania
19406-2772

a. What was inspected? The FDA Investigator reviewed sponsor monitor procedures and records for protocol EGF100151.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

The FDA Investigator did not issue a Form FDA 483. The audit did not identify significant errors or omissions from the data listings submitted in the NDA 22059.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data collected and maintained at the sponsor's site, as it pertains to the 4 clinical sites identified for audit in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810, associated with protocol EGF100151 appear consistent with that submitted to the agency as part and in support of NDA 22059, based on available information.

6.

a. What was inspected? The FDA Investigator reviewed CRO procedures and records for protocol EGF100151.

b. Limitations of inspection: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

c. General observations/commentary:

The FDA Investigator did not issue a Form FDA 483. The audit did not identify significant errors or omissions from the data listings submitted in the NDA 22059.

The EIR is currently being finalized and will be submitted to DSI upon completion. The observations noted above are based on the preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

d. Assessment of data integrity: The data collected and maintained at the monitor's site, as it pertains to the 4 clinical sites identified for audit in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810, associated with protocol EGF100151 appear consistent with that submitted to the agency as part and in support of NDA 22059, based on available information.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study data collected by Dr. Franco, Dr. Kalidas, Dr. Chan, and Dr. Jagiello-Gruszfeld appear reliable. The inspection of GlaxoSmithKline and _____ did not identify any significant issues.

Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Lauren Iacono-Connors
11/15/2006 04:49:23 PM
UNKNOWN

Leslie Ball
11/20/2006 08:05:55 PM
MEDICAL OFFICER

Robertson, Kim

From: Robertson, Kim
ent: Tuesday, October 17, 2006 7:10 PM
To: 'Rich.Swenson@gsk.com'
Subject: FW: NDA 22-059

Importance: High

Richard, I forgot to ask this, but would you please let me know how soon we can expect a response?

Thanks,
Kim

From: Robertson, Kim
Sent: Tuesday, October 17, 2006 7:03 PM
To: 'Rich.Swenson@gsk.com'
Subject: NDA 22-059
Importance: High

Richard, below is the information that our clinpharm reviewers are requesting from GSK with regard to your NDA 22-059:

Please submit the following data and datasets to support the QT analyses for study EGF10003 to your NDA submission:

- The exact NONMEM dataset used for the model development. This should be provided as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. The dataset should also include all covariates evaluated.
- NONMEM control streams (and also other model files) and output files should be provided in ASCII (*.txt) format for all major model building steps, e.g., base structural model, covariates models, final model, and validation model.

Thank you Richard,
Kim

Kim J. Robertson
Food and Drug Administration
Consumer Safety Officer
Division of Drug Oncology Products
(301) 796-1441
(301) 796-9845 (fax)
kim.robertson@fda.hhs.gov

REQUEST FOR CONSULTATION

(Office/Division): HFD-430 Office of Drug Safety
(DMETS) Attn: Scott Dallas/Diane Smith

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/DDOP/Kim Robertson

DATE October 2, 2006	IND NO.	NDA NO. 22-059	TYPE OF DOCUMENT New NDA-Clinical & Non-clinical	DATE OF DOCUMENT September 15, 2006
NAME OF DRUG Tykerb (lapatinib)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE November 10, 2006

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: DDOP is requesting DMETS to "Re-Review" the proposed proprietary name "Tykerb" for lapatinib for this NDA submission. The IND that the preliminary review was done was IND#61,362. DMETS had no objections to the use of this proprietary name based on DMETS' July 18, 2006 review. We wish to rule out any objections based upon approvals of other proprietary or established names at this time. The division plans to take an action on this NDA on December 15, 2006; 3 months prior to the actual PDUFA date of March 15, 2007.

SIGNATURE OF REQUESTOR Kim Robertson, CSO	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Kim Robertson
10/2/2006 05:00:22 PM
DMETS Consult sn:001, 002 & 003 (RRZ, RRM)

DSI CONSULT: Request for Clinical Inspections

Date: September 15, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCPI, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joseph Salewski, Acting Director, DSI, HFD-45
Kim J. Robertson, Consumer Safety Officer, HFD-150
Division of Drug Oncology Products

From: Robert L. Justice, M.D., Director, HFD-150

Subject: Request for Clinical Site Inspections
NDA 22-059
GlaxoSmithKline
Tykerb (lapatinib)

Protocol/Site Identification:

The NDA 22-059 is for a NME, lapatinib, which inhibits both ErbB1 and ErbB2 receptors. This NDA proposes the following new indication: Lapatinib in combination with capecitabine for the treatment of women with refractory advanced or metastatic breast cancer who have ErbB2 over expression and who have received prior therapy which included anthracyclines, taxanes, and trastuzumab. The key study for this NDA is EGF 100151, a randomized, open label, international, multicenter study to determine efficacy of the time to disease progression (TTP, primary endpoint) of lapatinib + capecitabine combination compared to capecitabine alone in proposed indication targeted patient population. Based on the IRC's first interim analyses and recommendation, the study was stopped for unexpected efficacy. A number of factors were considered for site selection, including accrual numbers, data documentation, number of responses (CRs and PRs), number of progression events and deaths and the discrepancy between investigators and IRC assessments regarding the number of responses and progression events. For this NDA, we proposed two sites for inspection (see table below). We will be happy to have our medical officer assist with the site audit for this NDA. We will need to have this inspection conducted within two months of receipt of this consult. (Previously discussed with Dr. Leslie Ball of DSI).

Request for Clinical Inspections

As discussed with you, the following protocols/sites essential for approval have been identified for inspection.

Indication	Lapatinib in combination with capecitabine for the treatment of women with refractory advanced or metastatic breast cancer who have documented ErbB2 over expression (IHC3+ or IHC 2+with FISH detection of ErbB2 gene amplification) and who have received prior therapy which included anthracyclines, taxanes, and trastuzumab	
Protocol #	EGF100151	
Study Title	A Phase III, Randomized, Open-Label, Multicenter Study Comparing GW572016 and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer	
Site Number/ Address	91482	91450
	Nottingham City Hospital Department of Clinical Oncology Next to Fraser Ward H Block 1st Floor Hucknall road Nottingham NG5 1PB, UK	ZOZ MSWiA z Warminsko Mazurskim Centrum Onkologii Onkologii w OlsztynieOddzial Chemioterapii Ul. Wojska Polskiego 37 10-228 Olsztyn, Poland
PI ID / Name	043954 / Dr. Stephen Chan,	040529/ Dr. Agnieszka Jagiello-Gruszfeld
Enrollment Number	13	11
CR + PR	IRC 2	3
	INV 4	3
TTP Events	IRC 5	6
	INV 7	3
OS Events	3	3
Subject ID	Cape ¹ 493, 1115, 1118, 1119	111, 114, 130, 134, 1261
	Lap + Cape ² 490, 494, 1116, 1117, 1123, 1124, 1125, 1126, 1338	113, 115, 128, 129, 132, 133

1. Capecitabine 2500 mg/m²/day
2. Lapatinib 1250 mg/day + capecitabine 2000 mg/m²/day

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

Domestic Inspections: NONE

We have requested inspections because (please check all that apply):

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

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data (Due to small number of U.S. accrual for Study EGF100151)
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other:

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 15, 2006. We intend to issue an action letter on this application by (division action goal date) December 15, 2006. The PDUFA due date for this application is March 13, 2007.

Should you require any additional information, please contact Kim Robertson.

Concurrence: (if necessary)

Amna Ibrahim, M.D., Medical Team Leader
Qin Ryan, M.D., Medical Reviewer
Robert L. Justice, M.D., Division Director (for foreign inspection requests only)

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/s/

Robert Justice
9/15/2006 05:51:19 PM

REQUEST FOR CONSULTATION

(Office/Division): HFD-110/Denise Hinton/Devi Kozeli
(RT)

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150/Kim Robertson

DATE
10-02-06

IND NO.

NDA NO.
22-059

TYPE OF DOCUMENT
New NDA; Clinical/Non-Clinical Submission

DATE OF DOCUMENT
September 15, 2006

NAME OF DRUG
Tykerb (lapatinib)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
November 3, 2006

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Our clinical pharmacology reviewer is requesting the review of submission NDA 22-059. The preliminary judgment on this NDA is that lapatinib may offer a significant advantage in therapy. For this reason, currently, the DDOP contemplates taking an action on this drug significantly before the full PDF time clock has elapsed. Thus, there likely will be a need for this consult to be completed more rapidly than would be the norm for a standard 6-month time clock NDA. Any information pertaining to this NDA can be found in the electronic document room (EDR).

SIGNATURE OF REQUESTOR
Kim Robertson

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

September 13, 2006



GlaxoSmithKline

Rebecca R. Hackett, Supervisor Consumer Safety
Division of Field Investigations
Office of Regulatory Affairs
Food and Drug Administration
International Operations Branch
5600 Fishers Lane, Room 13-71
Rockville, MD 20857

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Re: NDA 22-059; Tykerb® (lapatinib ditosylate) Tablets
Original Submission: CMC Field Copy

Dear Ms. Hackett:

SmithKline Beecham Corporation d/b/a GlaxoSmithKline hereby certifies that the contents of the Chemistry, Manufacturing and Controls Information for NDA 22-059, Tykerb™, Lapatinib Tablets, 250 mg were submitted electronically to the Division of Oncology Drug Products on September 13, 2006. Field Copy information can therefore be viewed electronically by your office.

Should you have any questions or comments regarding the contents of the Chemistry, Manufacturing, and Controls Information please do not hesitate to contact me at (919) 483-3426, fax (919) 483-5381 or via email at Sherry.L.Watson@gsk.com.

Please send all related correspondence to:

GlaxoSmithKline
ATTN: Sherry Watson
Five Moore Drive
Research Triangle Park, NC 27709-3398

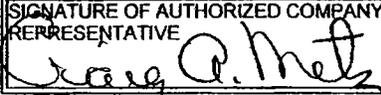
Sincerely,

A handwritten signature in cursive script that reads "Sherry L. Watson".

Sherry L. Watson
Director, New Submissions North America
Global CMC Regulatory Affairs

Rebecca R. Hackett
September 13, 2006
Page 2

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

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 Parker Holmes ONE FRANKLIN PLAZA 16TH AND RACE STREETS PHILADELPHIA PA 19101 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-059
2. TELEPHONE NUMBER 919-483-0920		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Tykerb (Lapatinib)		6. USER FEE I.D. NUMBER PD3006630
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, 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 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Vice President
		DATE 7/18/06
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$767,400.00		
Form FDA 3397 (12/03)		

(IBE PRMT CLOSE G) (Print Cover sheet)

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF DRUG ONCOLOGY PRODUCTS

HFD-150, FDA/CDER
5901-B Ammendale Road
Beltsville, MD 20705-1266

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PHONE: (301)796-1434 FAX: (301) 796-9845

TO: Richard Swenson, Ph.D., GSK

Fax: 610 787-7062

FROM: Kim Robertson, Consumer Safety Officer

Phone: (301) 796-1441

Total number of pages, including cover sheet 10

Date: 5-26-06

COMMENTS: Attached are the meeting minutes from our May 26, 2006 industry meeting

MEETING MINUTES

DATE: May 26, 2006

TIME: 2:00PM

LOCATION: Room 1417

IND/NDA: IND: 61,362 **Meeting Request Submission Date:** April 05, 2006

FDA Response Date: April 20, 2006

Briefing Document Submission Date: April 28, 2006

DRUG: Lapatinib in combination with Capecitabine

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of MEETING: Type B, Pre-NDA

Proposed Indication: _____

FDA PARTICIPANTS:

Robert L. Justice, M.D., Acting Div. Director
Ann Farrell, M.D., Acting Div. Deputy Director
Amna Ibrahim, M.D., Acting Clinical Team Leader (*Meeting Chair*)
Qin Ryan, M.D., Ph.D. Clinical Reviewer
Raji Sridhara, Ph.D., Statistical Team Leader, DBV
Shenghui Tang, Ph.D., Statistical Team Leader, DBV
Kim Robertson, Consumer Safety Officer (*Minutes Recorder/Facilitator*)

GLAXOSMITHKLINE PARTICIPANTS:

William Bushnell, M.S., Group Director, Statistics, Biomedical and Data Sciences
Susan Cousounis, B.S., Global Medical Writing Director, Medicines Develop. Ctr.-Clin. Onc.
Robert DiCicco, Pharm.D., Group Director, Medicines Development Center-Clin. Onc.
Beth Newstadt, M.S., Lead Scientist, Clinical Pharmacology and Discovery Medicine-Clin. Onc.
Paolo Paoletti, M.D., Senior Vice Pres., Medicine Development Ctr.-Clinical Oncology
Debasish Roychowdhury, M.D., Vice President, Medicines Develop. Center-Clinical Oncology
Steven H. Stein, M.D., Director, Medicines Development Center-Clinical Oncology
Richard Swenson, Ph.D., Director, Regulatory Affairs-Oncology
Robert Watson, M.B.A., Vice President, Regulatory Affairs-Oncology

GLAXOSMITHKLINE PARTICIPANTS (cont):
(via telephone)

Mark Berger, M.D., Director, Medicines Development Center-Oncology
Stephen D. Rubin, M.D., Director, Medicines Development Center-Oncology
Denise Zembryki, M.S., Lead Scientist, MDC

BACKGROUND:

EGF100151 is a randomized, open-label, multicenter, Study comparing Letrozole in combination with Capecitabine vs. Capecitabine alone to treat women with advanced or metastatic breast cancer whose tumors overexpress ErbB2 (IHC3+ or IHC2+ with FISH confirmation) and who have received prior therapies such as taxane, an anthracyclines and trastuzumab. Approximately 528 eligible female patients will be enrolled in this trial. The proposed dose plan is patients will receive either lapatinib (1,250 mg) once daily continuously in combination with capecitabine (2000 mg/m²/day) Days 1-14, every 21 days, or capecitabine (2,500mg/m²/day) Days 1-14, every 21 days. The primary endpoint is time to progression (TTP). The secondary endpoints are overall survival (OS), progression free survival (PFS), duration of response, and quality of life (QoL) (FACT-B and EQ-5D). At the interim analysis of primary endpoint, TTP was statistically significant and crossed O'Brian-Fleming boundary. The IDMC recommended stopping the study for efficacy. The study was stopped at April 3, 2006 with a total enrollment of 399 patients.

**APPEARS THIS WAY
ON ORIGINAL**

between GlaxoSmithKline and the FDA.

Clinical

1. The NDA will be primarily based on pivotal Study EGF100151 and supporting data from Study EGF10005. These are the key studies supporting efficacy for the lapatinib plus capecitabine combination. Based on the results from Study EGF100151, does FDA agree with the proposed indication listed below?

“Lapatinib, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress ErbB2

FDA Response: The exact wording of the indication will be a review issue.

Discussion Point: GSK agrees that further discussion is not necessary.

2. The primary evidence of efficacy of the combination will come from Phase 3 Study EGF100151. GSK has provided a Reporting Analysis Plan for Study EGF100151. Phase 1 study EGF10005 was designed to demonstrate the optimally tolerated regimen and provides supportive evidence of efficacy for the combination. Additional evidence of efficacy will come from lapatinib monotherapy Phase 2 studies EGF20002 and 20008. The efficacy results of these studies will be presented but not pooled in the Summary of Clinical Efficacy. Does the FDA agree with the proposed plan for the Summary of Clinical Efficacy?

FDA Response: Yes. We agree that the efficacy data should not be pooled from the two studies. For study EGF100151 efficacy data, you should submit assessments based on investigators' and independent review and also include analyses and explanations for discrepancies.

Discussion Point: GSK provided an example of an Excel spreadsheet that would be included in the application. This would appear to be acceptable and FDA may require additional information based on the review.

3. GSK intends to use a 15 November 2005 cutoff date for efficacy data from EGF10015 (interim analysis provided to IDMC) and intends for these results to serve as the basis for approval of this NDA. Does the FDA agree with the proposal to use a 15 November 2005 cut off date for efficacy data from EGF10015 (interim analysis provided to IDMC) and that these results will serve as the basis for approval of this NDA?

FDA Response: Yes. Please also submit an updated efficacy analysis of TTP and overall survival with the safety update.

Please plan to provide CRFs and disease assessment summaries upon FDA request during review.

Please clarify the following in your NDA efficacy report:

- a. **How many events in your interim analysis were based on symptomatic progressions? *GSK replied none.***
- b. **Were the analyses for the IDMC conducted by independent statisticians? *GSK replied yes.***
- c. **Was the Sponsor project statistician blinded from data provided to the IDMC? *GSK replied yes.***

Discussion Point: GSK proposes to submit the updated efficacy data within the first 2 months of the submission. This is acceptable to the Agency. FDA requests that data set includes an indicator variable that designates from which clinical cut-off date the data base was derived.

GSK agrees to provide CRFs and narratives for SAEs (narratives only), deaths (other than disease progression), discontinuations due to AEs on study 151 at the time of submission. GSK also agrees to provide other CRFs upon request for study 151.

4. As described in the "Endpoint Review Committee Charter", scans of patients are collected and processed by _____
_____ trains members of the Independent Review Committee (IRC) and archives the patient scans and IRC analysis forms. In the review of the NDA, it is anticipated FDA may require access to patient scans. To preserve the integrity of the independent review, GSK believes it would be appropriate for the Division to contact _____ directly for access to patient scans. Does the FDA agree to liaise with _____ to access patient scans during the review?

FDA Response: No. The applicant is ultimately responsible for the conduct of the independent review, and should provide scans and required information from the independent reviewer.

Discussion Point: GSK will provide data by a hard drive by _____ and will arrange training as needed.

5. Safety data for the combination of capecitabine/lapatinib will be based on data from Phase 3 study EGF100151 and Phase 1 study EGF10005 (total of 205 patients). Lapatinib monotherapy safety will be supported by pooled safety data from EGF20002 and EGF20008 (total of 307 patients).

In the summary of clinical safety, Phase 1 data will not be integrated with Phase 2 and 3 data.

Although there are other studies (mostly ongoing) in which lapatinib is given as monotherapy or in combination in patients with breast cancer and other solid tumors, only serious adverse events (SAEs) will be reported from these studies in the NDA (up to a clinical cutoff of 3 April 2006). A separate summary of cardiac safety also will be included in the summary of safety.

Does the FDA agree with the proposed plan for the Summary of Clinical Safety?

FDA Response: This may be acceptable. Information regarding any known SAEs related to lapatinib not observed in EGF100151 and EGF10005 should be provided in the NDA.

Discussion Point: GSK will include SAE information on all lapatinib studies.

6. GSK proposes to perform subset analyses based on age (65 years and older vs younger than 65 years) but does not propose to perform subset analyses on gender and race. The targeted patient population is women with breast cancer, and in our clinical studies approximately 80% to 90% of patients are Caucasian. Does the FDA agree that the only subset analysis of efficacy will be performed with regard to age (and not gender and race)?

FDA Response: No. Please also provide analyses by race, although we understand that there were few non-Caucasians in the study.

Discussion Point: GSK agrees and no further discussion is necessary.

7. Preclinical data do not show any signals to suggest QTc concerns (dog cardiac Purkinje fiber). A review of the clinical safety database at present supports an acceptable risk/benefit ratio with respect to cardiovascular safety. Specifically there does not appear to be a signal with respect to any pro-arrhythmic effect.

Given the potential genotoxicity and cardiotoxicity (decrease ejection fraction), a definitive QTc interval study with lapatinib will not be part of the NDA due to the limitation of administering the proposed labeled doses to healthy volunteers.

Does the FDA agree a QTc interval study will not be included in NDA?

FDA Response: You will need to more definitively address lapatinib's effect on QTc in patients as you progress in drug development. The NDA should include a summary and modeling of all of the human QTc data accumulated.

Discussion Point: GSK plans to provide QTc data that are available within the application. GSK also agrees to propose additional studies to be discussed with the division.

Clinical Pharmacology

8. In the Special Protocol Assessment for Study EGF100151 (November 2003), FDA requested pharmacokinetic (PK) data on the effect of capecitabine on lapatinib metabolism (and vice versa) *in the intended population*. GSK believes the PK data from the formal PK Study EGF10005 in patients with solid tumors is applicable to the indicated population and no additional studies are planned. Does the FDA agree with this proposal concerning pharmacokinetic data?

FDA Response: We agree that the population studied in EGF10005 may provide applicable information. Without more details regarding the study design and conduct, we cannot conclude that the study is adequate for making conclusions regarding whether a drug interaction occurs.

Discussion Point: See meeting minutes of May 23, 2006 for all PK issues.

9. An absolute bioavailability study in humans has not yet been conducted due to difficulties in developing a viable, safe intravenous formulation. The NDA will not contain a human absolute bioavailability study. Does the FDA agree the NDA can be approved without data on absolute bioavailability of lapatinib tablets?

FDA Response: We agree that absolute bioavailability data is not essential for NDA filing. The adequacy of the relative bioavailability data acquired with oral suspensions to support NDA filing is a review issue.

Discussion Point: See meeting minutes of May 23, 2006 for all PK issues.

10. GSK will provide complete study reports for key clinical pharmacology studies (described in a table of studies showing status), one or two page summaries for ongoing GSK sponsored studies, and a tabular display of NCI-CTEP studies showing status and summary outcome information if available. Does the FDA agree with the plan regarding reporting Clinical Pharmacology studies?

FDA Response: The table of studies (Appendix 4) does not describe the ongoing GSK sponsored studies or the NCI-CTEP studies. We cannot agree that one or two page summaries or a tabular display will be adequate when we do not know the content of the studies.

We recommend that all raw pharmacokinetic and pharmacodynamic data, together with covariate data, be submitted in the NDA as a SAS transport file(s).

Discussion Point: This appears acceptable to the Agency.

Administrative

11. Advanced/metastatic breast cancer does not appear to any significant extent in patients younger than 16 years of age. GSK will request a waiver for pediatric studies. Does the FDA agree?

FDA Response: You may submit your request for pediatric waiver with your NDA application or separately.

Discussion Point: GSK agrees and no further discussion is necessary

12. GSK plans to submit the lapatinib NDA as an electronic submission in CTD format. Is there a need for any paper copies of the submission or will this be acceptable as an entirely electronic NDA in CTD format?

FDA Response: An electronic submission will be acceptable.

Discussion Point: GSK agrees and no further discussion is necessary

13. GSK proposes to submit CRFs and case narratives for deaths (due to events other than disease progression) and patients whose adverse events resulted in discontinuation (on study through 30 days post treatment) in pivotal Study EGF100151 only. For the other studies, case report forms and narratives will be available upon request. Does the FDA agree?

FDA Response: Other CRFs and narratives should be available within a short period of time (such as 48 hours) on request.

Discussion Point: GSK agrees and no further discussion is necessary

14. GSK will submit the NDA 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 Safety (ISS); thus, no separate ISE or ISS will be included in this submission. Does the FDA agree 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: No. Please submit an ISE and an ISS in Module 5.

Discussion Point: GSK clarified that the clinical summaries of safety and efficacy will contain the same information as ISS and ISE. The review team will discuss this issue with the IT department. The Agency will contact GSK as soon as possible regarding this issue.

15. In advance of its review of the lapatinib NDA, FDA may not be able to provide us with insight into the likelihood of lapatinib appearing before the Oncology Drug Advisory Committee (ODAC). Nevertheless, it would be helpful to GSK if the Division would share with us your current thinking on what determines the need for an application to appear before ODAC.

FDA Response: We cannot comment on this issue at this time.

Discussion Point: There were no comments.

16. On 28 October 2003, FDA granted Fast Track designation to lapatinib in the targeted patient population. GSK may submit this application in two stages: the initial submission will contain all components of the CTD aside from the CMC information. Approximately 2-3 months later, GSK would complete the application with the CMC information. At our pre-NDA meeting, GSK will provide FDA with an update to our plans for submission of a Rolling NDA including dates for completing the application. Is this acceptable to the Division?

FDA Response: Yes.

Discussion Point: GSK stated all but CMC information will be targeted for submission August 15, 2006. CMC information will be submitted approximately September 15, 2006.

ADDITIONAL FDA COMMENTS:

CHEMISTRY/MANUFACTURING/CONTROLS:

All manufacturing, testing, packaging, and labeling sites should be ready for inspection at the time of submission of the CMC portion of the NDA.

CLINICAL/CLINICAL PHARMACOLOGY:

Will an analysis of efficacy and safety as a function of CYP2C19 status be submitted as part of the NDA? Please clarify recent press releases regarding the use of CYP2C19 status for dosing.

Discussion Point: See meeting minutes from the May 23, 2006 biopharm discussion.

OFFICE of SURVEILLANCE and EPIDEMIOLOGY COMMENTS:

- **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.**

Meeting Adjourned: 3:05PM



IND 61,362

SmithKlineBeecham d/b/a GlaxoSmithKline
2301 Renaissance Blvd., Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Attention: Richard Swenson, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Swenson:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GW572016.

Additionally, we refer to your August 26, 2003 request, serial number 092, for a special clinical protocol assessment. The GW572016 protocol EGF100151 is entitled "A Phase 3, Randomized, Open-Label, Multicenter Study Comparing GW572016 and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Clinical Question #1: (TTP as the primary endpoint)

In this refractory patient population, does the Division agree time to disease progression is an appropriate primary endpoint?

FDA Response:

TTP could be an acceptable endpoint in the setting of advanced/metastatic disease refractory to available therapy, at least to support accelerated approval. However, we note that the definition of TTP, as proposed in your protocol, includes not only radiographic progression, but also clinical deterioration. This may introduce bias. We recommend a definition of TTP based primarily on radiographic considerations.

If clinical criteria will be a component of the definition of progression they should be objective, pre-specified, and captured in the CRF.

Clinical Question #2: (Proposed Indication)

Provided the study objective is met, would this trial allow for full approval of GW572016 with the following indication: "GW572016 in combination with capecitabine is indicated for the treatment of patients with refractory advanced or metastatic breast cancer who have ErbB2 overexpression"

FDA Response:

Whether the TTP results will support full approval will be a review issue and will depend upon a number of factors, such as the size and precision of the estimated effect and whether FDA views improvement in TTP as an established surrogate for clinical benefit in the metastatic breast cancer setting. FDA plans to discuss this issue in workshops and ODAC meetings in the coming year. See also response to #1.

Due to these concerns, we recommend that the study be powered for survival.

Clinical Question #3: (Capecitabine Regimen)

Does the FDA agree with the starting dose of capecitabine of 2500 mg/m²/day proposed for this study?

FDA Response:

Yes. However, after discussion with external consultants and because of concerns expressed in your meeting package regarding toxicity, we would support a design using a dose of 2000 mg/ m²/day in both arms.

Additional Clinical Comment:

Please submit a sample consent form and case report form for review.

Statistical Question #1: (Patients not previously exposed to trastuzumab)

Does the FDA agree that the primary focus for statistical inference should be based on the Intent-to-Treat population of all randomized patients?

FDA Response:

We agree that the primary analysis should be based on the ITT population. However, we recommend that you stratify the patient population at randomization by prior trastuzumab therapy. It is our understanding that the proposed primary inference will be based on

stratified log-rank test (including stage of disease and site of disease as stratification factors).

Whether or not prior trastuzumab therapy is incorporated as a stratification factor for randomization, balance between the study arms for factors which may influence outcome will be a review issue.

Statistical Question #2: (Accelerated approval based on interim analysis)

If the results of the interim analysis indicate that there is compelling evidence of superior response rates in the GW572016 plus capecitabine group, but the interim analysis of TTP data indicate that the study should continue to its planned conclusion, would submission of these data be acceptable for accelerated approval?

FDA Response:

The decision whether to file the application will be based primarily on quality and strength of evidence of the data at the interim analysis. However, we have concerns that the study may not be able to complete accrual if the interim results are positive. We recommend that the accrual of patients be completed prior to submission for accelerated approval.

See also response to clinical questions 1 and 2.

Statistical Question #3: (TTP vs PFS as the primary endpoint)

GSK would appreciate the FDA perspective regarding the arguments against the use of TTP and those in favor of PFS. Does the FDA prefer TTP to PFS in registration-designed clinical studies?

FDA Response:

In general we prefer TTP to PFS. In well conducted studies with an adequate assessment plan there should be few deaths prior to progression, in which case TTP and PFS are virtually identical. Although there is no ideal way to analyze deaths occurring prior to documentation of progression, in the absence of objective progression prior to death (e.g. lost to follow-up, change of treatment), the time to progression should be censored at the last tumor assessment date. Also, since the study is not blinded, a blinded independent assessment of progression may be required.

Additional Statistical Comments:

1. Please specify the type I error allocation for interim and final analyses while maintaining an over all type I error at 0.025 (one-sided).

2. If sample size re-estimation will be considered based on the interim analysis, please specify the methodology that will be used.
3. Secondary efficacy analyses are considered as exploratory and hypotheses generating. No efficacy claims can be made with respect to secondary efficacy endpoints.

Clinical Pharmacology and Biopharmaceutics Comments:

1. Pharmacokinetics. You should plan to assess the effect of capecitabine on the pharmacokinetics of GW572016 in this patient population, and vice versa.
2. Please submit a list of completed and planned clinical pharmacology and biopharmaceutics studies for GW572016.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our draft "Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

{See appended electronic signature page}

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

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/s/

Richard Pazdur
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