# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-059**

# APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-059

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

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

Dear Dr. Swenson:

Please refer to your new drug application (NDA) dated September 13, 2006, received September 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TYKERB® (lapatinib) tablets, 250 mg.

We acknowledge receipt of your submissions dated October 4, 11, 23, 26, 30 and 31, 2006; November 2, 9, 10 (2), 15, 17 (3), 21 (2), 27, and 30, 2006; December 1, 8, 13, 18, and 22 (5), 2006; January 9, 11, 18, 19, 24, and 29, 2007; February 1, 6 (2), 26, 2007; March 7 (2), 8 (2), and 12, 2007.

This new drug application provides for the use of TYKERB® in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

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

We remind you of your postmarketing study commitments in your submission dated March 7, 2007. These commitments are listed below.

1. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 3A4 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

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| Protocol Submission: | October 1, 2005 |
| Study Start: | Ongoing |
| Final Report Submission: | June 2008 |

2. **Description of Commitment:** Based upon the ability of lapatinib to act as a CYP 2C8 inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

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| Protocol Submission: | October 7, 2002 |
| Study Start: | Ongoing |
| Final Report Submission: | June 2007 |

3. **Description of Commitment:** Based upon the ability of lapatinib to act as a Pgp inhibitor in vitro, GSK agrees to perform an in vivo drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

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| Protocol Submission: | September 2007 |
| Study Start: | November 2007 |
| Final Report Submission: | December 2009 |

4. **Description of Commitment:** GSK commits to submitting the results of the survival analysis of Study EGF100151 at 75% of the events.

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| Protocol Submission: | November 2003 |
| Study Start: | Ongoing |
| Final Report Submission: | June 2008 |

All applications for new active ingredients, new dosage forms, new indications, new routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, and for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-059**." Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text/submitted labeling dated March 13, 2007. Upon

receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

Promotional materials should be submitted, in duplicate, directly to:

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

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

As discussed in our November 16, 2006 teleconference, your proposed Chemistry, Manufacturing and Controls (CMC) Regulatory Agreement, submitted as part of the CMC pilot program, was not received and is not part of this approval action. Existing regulations and guidances should be followed, as appropriate, for all post-approval CMC changes.

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

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

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

Sincerely,

*{See appended electronic signature page}*

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

Enclosure-Label

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

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/s/

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Richard Pazdur

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