CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022059Orig1s017

Trade Name:	TYKERB
Generic or Proper Name:	lapatinib
Sponsor:	SmithKline Beecham (Cork) Ltd., Ireland d/b/a GlaxoSmithKlein
Approval Date:	October 18, 2013
Indication:	TYKERB, a kinase inhibitor, is indicated in combination with: • capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine. • letrozole for the treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer that overexpress the HER2 receptor for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022059/S-016/S-017

SUPPLEMENT APPROVAL

SmithKline Beecham (Cork) Ltd., Ireland d/b/a GlaxoSmithKline
Attention: Richard Swenson, PhD
Senior Director, Global Regulatory Affairs
1250 S. Collegeville Road, UP4110
Collegeville, PA 19426

Dear Dr. Swenson:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 26, 2012, for Supplement 016 (S-016) and December 18, 2012, for Supplement 017 (S-017), received November 28, 2012, and December 19, 2012, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tykerb® (lapatinib) Tablets 250 mg.

We acknowledge receipt of your amendments dated December 18 (2), 2012, January 11, February 6, 8, 12 (2), 13, 21, and 27, July 2 (2), August 22, September 13 (2), 27 (2), and October 11 (2), and 17 (2), 2013.

"Prior Approval" supplemental new drug application S-016 provides for a change to the approved indication for Tykerb® when used in combination with capecitibine.

"Prior Approval" supplemental new drug application S-017 provides for changes to the package insert to include increased risk of hepatotoxicity in persons with HLA risk alleles based on pharmacogenetics data.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for S-016 because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children.

Because none of these criteria apply to S-017, you are exempt from this requirement for S-017.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Rajesh Venugopal, Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Anthony J. Murgo, MD, MS
Acting Director, Division of Oncology Products 1
Associate Office Director for Regulatory Science
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ANTHONY J MURGO
10/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022059Orig1s017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYKERB safely and effectively. See full prescribing information for TYKERB.

TYKERB (lapatinib) tablets, for oral use
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain *[see Warnings and Precautions (5.2)]*.

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	10/2013
Dosage and Administration, Dose Modification Guidelines (2.2)	12/2012
Warnings and Precautions, Diarrhea (5.4)	06/2013

----------INDICATIONS AND USAGE----------

TYKERB, a kinase inhibitor, is indicated in combination with: (1)

- capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
  Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine.
- letrozole for the treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

---------- DOSAGE AND ADMINISTRATION ----------

The recommended dosage of TYKERB for advanced or metastatic breast cancer is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. (2.1)

The recommended dose of TYKERB for hormone receptor-positive, HER2-positive metastatic breast cancer is 1,500 mg (6 tablets) given orally once daily continuously in combination with letrozole. When TYKERB is coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily. (2.1)

- TYKERB should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. (2.1)
- TYKERB should be taken once daily. Do not divide daily doses of TYKERB. (2.1, 12.3)
- Modify dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

250 mg tablets (3)

----------CONTRAINDICATIONS----------

Known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Decreases in left ventricular ejection fraction (LVEF) have been reported. Confirm normal LVEF before starting TYKERB and continue evaluations during treatment. (5.1)
- Lapatinib has been associated with hepatotoxicity. Monitor liver function tests before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. Discontinue and do not restart TYKERB if patients experience severe changes in liver function tests. (5.2)
- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.3, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.4)
- Lapatinib has been associated with interstitial lung disease and pneumonitis. Discontinue TYKERB if patients experience severe pulmonary symptoms. (5.5)
- Lapatinib may prolong the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.6, 12.4)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.7)

---------- ADVERSE REACTIONS ----------

The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. The most common (≥20%) adverse reactions during treatment with TYKERB plus letrozole were diarrhea, rash, nausea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- TYKERB is likely to increase exposure to concomitantly administered drugs which are substrates of CYP3A4, CYP2C8, or P-glycoprotein (ABCB1). (7.1)
- Avoid strong CYP3A4 inhibitors. If unavoidable, consider dose reduction of TYKERB in patients coadministered a strong CYP3A4 inhibitor. (2.2, 7.2)
- Avoid strong CYP3A4 inducers. If unavoidable, consider gradual dose increase of TYKERB in patients coadministered a strong CYP3A4 inducer. (2.2, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain *[see Warnings and Precautions (5.2]*.

1 INDICATIONS AND USAGE

TYKERB® is indicated in combination with:

- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

  Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine.
- letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

TYKERB in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

HER2-Positive Metastatic Breast Cancer: The recommended dose of TYKERB is 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing the daily dose is not recommended *[see Clinical Pharmacology (12.3)]*. Capecitabine should be taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer: The recommended dose of TYKERB is 1,500 mg given orally once daily continuously in combination with letrozole. When coadministered with TYKERB, the recommended dose of letrozole is 2.5 mg once daily. TYKERB should be taken at least one hour before or one hour after a meal. The dose of TYKERB should be once daily (6 tablets administered all at once); dividing the daily dose is not recommended *[see Clinical Pharmacology (12.3)]*.

2.2 Dose Modification Guidelines

Cardiac Events: TYKERB should be discontinued in patients with a decreased left

ventricular ejection fraction (LVEF) that is Grade 2 or greater by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v3) and in patients with an LVEF that drops below the institution's lower limit of normal *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*. TYKERB in combination with capecitabine may be restarted at a reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at a reduced dose of 1,250 mg/day after a minimum of 2 weeks if the LVEF recovers to normal and the patient is asymptomatic.

Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range and should be considered. However, there are no clinical data with this dose adjustment in patients with severe hepatic impairment.

Diarrhea: TYKERB should be interrupted in patients with diarrhea which is NCI CTCAE Grade 3 or Grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting ≥NCI CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration). TYKERB may be reintroduced at a lower dose (reduced from 1,250 mg/day to 1,000 mg/day or from 1,500 mg/day to 1,250 mg/day) when diarrhea resolves to Grade 1 or less. TYKERB should be permanently discontinued in patients with diarrhea which is NCI CTCAE Grade 4 *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the lapatinib dose is adjusted upward to the indicated dose *[see Drug Interactions (7.2)]*.

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's wort). If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day up to 5,500 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered. However, there are no clinical

data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the lapatinib dose should be reduced to the indicated dose *[see Drug Interactions (7.2)]*.

Other Toxicities: Discontinuation or interruption of dosing with TYKERB may be considered when patients develop ≥Grade 2 NCI CTCAE toxicity and can be restarted at the standard dose of 1,250 or 1,500 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then TYKERB in combination with capecitabine should be restarted at a lower dose (1,000 mg/day) and in combination with letrozole should be restarted at a lower dose of 1,250 mg/day.

See manufacturer's prescribing information for the coadministered product dosage adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

3 DOSAGE FORMS AND STRENGTHS

250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one side.

4 CONTRAINDICATIONS

TYKERB is contraindicated in patients with known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Left Ventricular Ejection Fraction

TYKERB has been reported to decrease LVEF *[see Adverse Reactions (6.1)]*. In clinical trials, the majority (>57%) of LVEF decreases occurred within the first 12 weeks of treatment; however, data on long-term exposure are limited. Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institution's normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the institution's normal limits *[see Dosage and Administration (2.2)]*.

5.2 Hepatotoxicity

Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If changes in liver function are severe, therapy with TYKERB should be discontinued and patients should not be retreated with TYKERB *[see Adverse Reactions (6.1)]*.

5.3 Patients With Severe Hepatic Impairment

If TYKERB is to be administered to patients with severe pre-existing hepatic impairment, dose reduction should be considered *[see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]*. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB *[see Warnings and Precautions (5.2)]*.

5.4 Diarrhea

Diarrhea has been reported during treatment with TYKERB *[see Adverse Reactions (6.1)]*. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs early during treatment with TYKERB, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib-induced diarrhea is usually low-grade, with severe diarrhea of NCI CTCAE Grades 3 and 4 occurring in <10% and <1% of patients, respectively. Early identification and intervention is critical for the optimal management of diarrhea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhea with anti-diarrheal agents (such as loperamide) after the first unformed stool is recommended. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and interruption or discontinuation of therapy with TYKERB *[see Dosage and Administration (2.2)]*.

5.5 Interstitial Lung Disease/Pneumonitis

Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies *[see Adverse Reactions (6.1)]*. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease or pneumonitis. TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are ≥Grade 3 (NCI CTCAE).

5.6 QT Prolongation

QT prolongation was observed in an uncontrolled, open-label, dose-escalation study of lapatinib in advanced cancer patients *[see Clinical Pharmacology (12.4)]*. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration.

5.7 Use in Pregnancy

TYKERB can cause fetal harm when administered to a pregnant woman. Based on findings in animals, TYKERB is expected to result in adverse reproductive effects. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth *[see Use in Specific Populations (8.1)]*.

There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this drug is used

during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

HER2-Positive Metastatic Breast Cancer: The safety of TYKERB has been evaluated in more than 12,000 patients in clinical trials. The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in 198 patients in a randomized, Phase 3 trial *[see Clinical Studies (14.1)]*. Adverse reactions which occurred in at least 10% of patients in either treatment arm and were higher in the combination arm are shown in Table 1.

The most common adverse reactions (>20%) during therapy with TYKERB plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysesthesia and rash), and fatigue. Diarrhea was the most common adverse reaction resulting in discontinuation of study medication.

The most common Grade 3 and 4 adverse reactions (NCI CTCAE v3) were diarrhea and palmar-plantar erythrodysesthesia. Selected laboratory abnormalities are shown in Table 2.

Table 1. Adverse Reactions Occurring in ≥10% of Patients

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day (N = 198)			Capecitabine 2,500 mg/m^2/day (N = 191)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Reactions	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash[b]	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

[b] Grade 3 dermatitis acneiform was reported in <1% of patients in the group receiving TYKERB plus capecitabine.

Table 2. Selected Laboratory Abnormalities

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day			Capecitabine 2,500 mg/m^2/day		
	All Grades[a]	**Grade 3**	**Grade 4**	**All Grades**[a]	**Grade 3**	**Grade 4**
Parameters	**%**	**%**	**%**	**%**	**%**	**%**
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Platelets	18	<1	0	17	<1	<1
Neutrophils	22	3	<1	31	2	1
Hepatic						
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0
ALT	37	2	0	33	1	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hormone Receptor-Positive, Metastatic Breast Cancer: In a randomized clinical trial of patients (N = 1,286) with hormone receptor-positive, metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. In this trial, the safety profile of TYKERB was consistent with previously reported results from trials of TYKERB in the advanced or metastatic breast cancer population. Adverse reactions which occurred in at least 10% of patients in either treatment arm and were higher in the combination arm are shown in Table 3. Selected laboratory abnormalities are shown in Table 4.

Table 3. Adverse Reactions Occurring in ≥10% of Patients

	TYKERB 1,500 mg/day + Letrozole 2.5 mg/day (N = 654)			Letrozole 2.5 mg/day (N = 624)		
Reactions	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**	**All Grades[a] %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Anorexia	11	<1	0	9	<1	0
Skin and subcutaneous tissue disorders						
Rash[b]	44	1	0	13	0	0
Dry skin	13	<1	0	4	0	0
Alopecia	13	<1	0	7	0	0
Pruritus	12	<1	0	9	<1	0
Nail Disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

[b] In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment arm had rash under "Infections and infestations"; none were Grade 3 or 4.

Table 4. Selected Laboratory Abnormalities

	TYKERB 1,500 mg/day + Letrozole 2.5 mg/day			Letrozole 2.5 mg/day		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Hepatic Parameters	**%**	**%**	**%**	**%**	**%**	**%**
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0
Total Bilirubin	22	<1	<1	11	1	<1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Decreases in Left Ventricular Ejection Fraction: Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who received combination treatment with TYKERB/capecitabine, 3 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTCAE v3) *[see Warnings and Precautions (5.1)]*. Among 654 patients who received combination treatment with TYKERB/letrozole, 26 patients experienced Grade 1 or 2 and 6 patients had Grade 3 or 4 LVEF adverse reactions.

Hepatotoxicity: TYKERB has been associated with hepatotoxicity *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Interstitial Lung Disease/Pneumonitis: TYKERB has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies *[see Warnings and Precautions (5.5)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TYKERB. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions including anaphylaxis *[see Contraindications (4)]*.

Skin and Subcutaneous Tissue Disorders: Nail disorders including paronychia.

7 DRUG INTERACTIONS

7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems

Lapatinib inhibits CYP3A4, CYP2C8, and P-glycoprotein (P-gp, ABCB1) in vitro at clinically relevant concentrations and is a weak inhibitor of CYP3A4 in vivo. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing TYKERB concurrently with medications with narrow therapeutic windows that are

substrates of CYP3A4, CYP2C8, or P-gp. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes in vitro, however, the clinical significance is unknown.

Midazolam: Following coadministration of TYKERB and midazolam (CYP3A4 substrate), 24-hour systemic exposure (AUC) of orally administered midazolam increased 45%, while 24-hour AUC of intravenously administered midazolam increased 22%.

Paclitaxel: In cancer patients receiving TYKERB and paclitaxel (CYP2C8 and P-gp substrate), 24-hour systemic exposure (AUC) of paclitaxel was increased 23%. This increase in paclitaxel exposure may have been underestimated from the in vivo evaluation due to study design limitations.

Digoxin: Following coadministration of TYKERB and digoxin (P-gp substrate), systemic AUC of an oral digoxin dose increased approximately 2.8-fold. Serum digoxin concentrations should be monitored prior to initiation of TYKERB and throughout coadministration. If digoxin serum concentration is >1.2 ng/mL, the digoxin dose should be reduced by half.

7.2 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly *(see Ketoconazole and Carbamazepine sections, below)*. Dose adjustment of lapatinib should be considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes *[see Dosage and Administration (2.2)]*.

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to lapatinib was decreased approximately 72%.

7.3 Drugs That Inhibit Drug Transport Systems

Lapatinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If TYKERB is administered with drugs that inhibit P-gp, increased concentrations of lapatinib are likely, and caution should be exercised.

7.4 Acid-Reducing Agents

The aqueous solubility of lapatinib is pH dependent, with higher pH resulting in lower solubility. However, esomeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 7 days, did not result in a clinically meaningful reduction in lapatinib steady-state exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.7)]*.

Based on findings in animals, TYKERB can cause fetal harm when administered to a

pregnant woman. Lapatinib administered to rats during organogenesis and through lactation led to death of offspring within the first 4 days after birth. When administered to pregnant animals during the period of organogenesis, lapatinib caused fetal anomalies (rats) or abortions (rabbits) at maternally toxic doses. There are no adequate and well-controlled studies with TYKERB in pregnant women. Women should be advised not to become pregnant when taking TYKERB. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a study where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine), 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human clinical exposure based on AUC).

Lapatinib was studied for effects on embryo-fetal development in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects; however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification) occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure, respectively, based on AUC following 1,250 mg dose of lapatinib plus capecitabine) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased fetal body weights and minor skeletal variations.

8.3 Nursing Mothers

It is not known whether lapatinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TYKERB, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TYKERB in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Lapatinib pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing hemodialysis. There is no experience with TYKERB in patients with severe renal impairment. However, renal impairment is unlikely to affect the pharmacokinetics of lapatinib given that less than 2% (lapatinib and metabolites) of an administered dose is eliminated by the kidneys.

8.7 Hepatic Impairment

The pharmacokinetics of lapatinib were examined in subjects with pre-existing moderate (n = 8) or severe (n = 4) hepatic impairment (Child-Pugh Class B/C, respectively) and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose increased approximately 14% and 63% in subjects with moderate and severe pre-existing hepatic impairment, respectively. Administration of TYKERB in patients with severe hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction should be considered for patients with severe pre-existing hepatic impairment *[see Dosage and Administration (2.2)]*. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB *[see Warnings and Precautions (5.2)]*.

10 OVERDOSAGE

There is no known antidote for overdoses of TYKERB. The maximum oral doses of lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials and could result in increased toxicity. Therefore, missed doses should not be replaced and dosing should resume with the next scheduled daily dose.

Asymptomatic and symptomatic cases of overdose have been reported. The doses ranged from 2,500 to 9,000 mg daily and where reported, the duration varied between 1 and 17 days. Symptoms observed include lapatinib-associated events *[see Adverse Reactions (6.1)]* and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG), and/or mucosal inflammation.

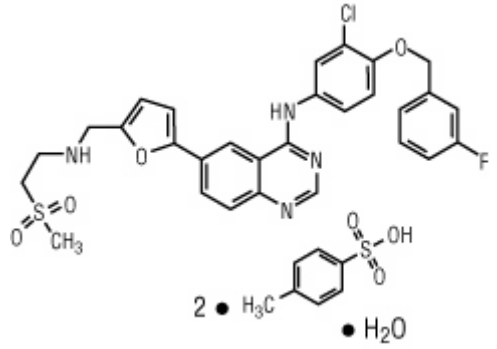
Because lapatinib is not significantly renally excreted and is highly bound to plasma proteins, hemodialysis would not be expected to be an effective method to enhance the elimination of lapatinib.

Treatment of overdose with TYKERB should consist of general supportive measures.

11 DESCRIPTION

Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$ $(C_7H_8O_3S)_2$ H_2O and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the

following chemical structure:



Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is 0.001 mg/mL at 25°C.

Each 250 mg tablet of TYKERB contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base.

The inactive ingredients of TYKERB are: **Tablet Core:** Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat: FD&C yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lapatinib is a 4-anilinoquinazoline kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor Type 2 (HER2 [ErbB2]) receptors (estimated K_i^{app} values of 3nM and 13nM, respectively) with a dissociation half-life of ≥300 minutes. Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models.

An additive effect was demonstrated in an in vitro study when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination in the 4 tumor cell lines tested. The growth inhibitory effects of lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib retained significant activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium in vitro. These in vitro findings suggest non-cross-resistance between these two agents.

Hormone receptor-positive breast cancer cells (with ER [Estrogen Receptor] and/or PgR [Progesterone Receptor]) that coexpress the HER2 tend to be resistant to established endocrine therapies. Similarly, hormone receptor-positive breast cancer cells that initially lack EGFR or HER2 upregulate these receptor proteins as the tumor becomes resistant to endocrine therapy.

12.3 Pharmacokinetics

Absorption: Absorption following oral administration of TYKERB is incomplete and variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours

after administration. Daily dosing of TYKERB results in achievement of steady-state within 6 to 7 days, indicating an effective half-life of 24 hours.

At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval) values of C_{max} were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.h/mL (23.4 to 56 mcg.h/mL).

Divided daily doses of TYKERB resulted in approximately 2-fold higher exposure at steady state (steady-state AUC) compared to the same total dose administered once daily.

Systemic exposure to lapatinib is increased when administered with food. Lapatinib AUC values were approximately 3- and 4-fold higher (C_{max} approximately 2.5- and 3-fold higher) when administered with a low-fat (5% fat-500 calories) or with a high-fat (50% fat-1,000 calories) meal, respectively.

Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast cancer-resistance protein (BCRP, ABCG2) and P-glycoprotein (P-gp, ABCB1). Lapatinib has also been shown to inhibit P-gp, BCRP, and the hepatic uptake transporter OATP 1B1, in vitro at clinically relevant concentrations.

Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which accounts for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma.

Elimination: At clinical doses, the terminal phase half-life following a single dose was 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of 27% (range 3% to 67%) of an oral dose.

Effects of Age, Gender, or Race: Studies of the effects of age, gender, or race on the pharmacokinetics of lapatinib have not been performed.

12.4 QT Prolongation

The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-label, dose-escalation study in advanced cancer patients. Eighty-one patients received daily doses of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and Day 14 to evaluate the effect of lapatinib on QT intervals. Analysis of the data suggested a consistent concentration-dependent increase in QTc interval.

12.5 Pharmacogenomics

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DQA1*02:01 or DRBI*07:01 allele carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately 15% to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese

populations. Liver function should be monitored in all patients receiving therapy with TYKERB regardless of genotype.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies with lapatinib are ongoing.

Lapatinib was not clastogenic or mutagenic in the Chinese hamster ovary chromosome aberration assay, microbial mutagenesis (Ames) assay, human lymphocyte chromosome aberration assay or the in vivo rat bone marrow chromosome aberration assay at single doses up to 2,000 mg/kg. However, an impurity in the drug product (up to 4 ppm or 8 mcg/day) was genotoxic when tested alone in both in vitro and in vivo assays.

There were no effects on male or female rat mating or fertility at doses up to 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However, when female rats were given oral doses of lapatinib during breeding and through the first 6 days of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and in the fetal body weights at ≥60 mg/kg/day (approximately 6.4 times and 3.3 times the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine, respectively).

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) overexpressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously) plus capecitabine 2,000 mg/m^2/day on Days 1-14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m^2/day on Days 1-14 every 21 days. The endpoint was time to progression (TTP). TTP was defined as time from randomization to tumor progression or death related to breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+ (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes, and trastuzumab.

Efficacy analyses 4 months after the interim analysis are presented in Table 5, Figure 1, and Figure 2.

Table 5. Efficacy Results

	Independent Assessment[a]		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day	**Capecitabine 2,500 mg/m^2/day**	**TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day**	**Capecitabine 2,500 mg/m^2/day**
	(N = 198)	**(N = 201)**	**(N = 198)**	**(N = 201)**
Number of TTP events	82	102	121	126
Median TTP, weeks (25th, 75th, Percentile), weeks	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)
Hazard Ratio (HR) (95% CI) *P* value	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
Response Rate (%) (95% CI)	23.7 (18.0, 30.3)	13.9 (9.5, 19.5)	31.8 (25.4, 38.8)	17.4 (12.4, 23.4)

TTP = Time to progression.

[a] The time from last tumor assessment to the data cut-off date was >100 days in approximately 30% of patients in the independent assessment. The pre-specified assessment interval was 42 or 84 days.

Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to Progression

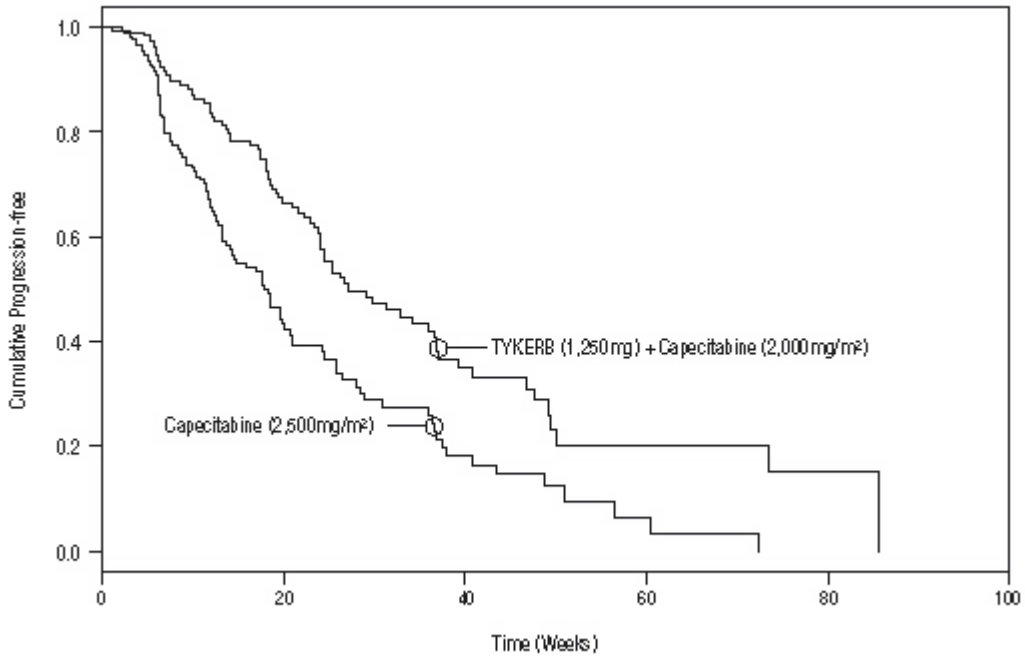
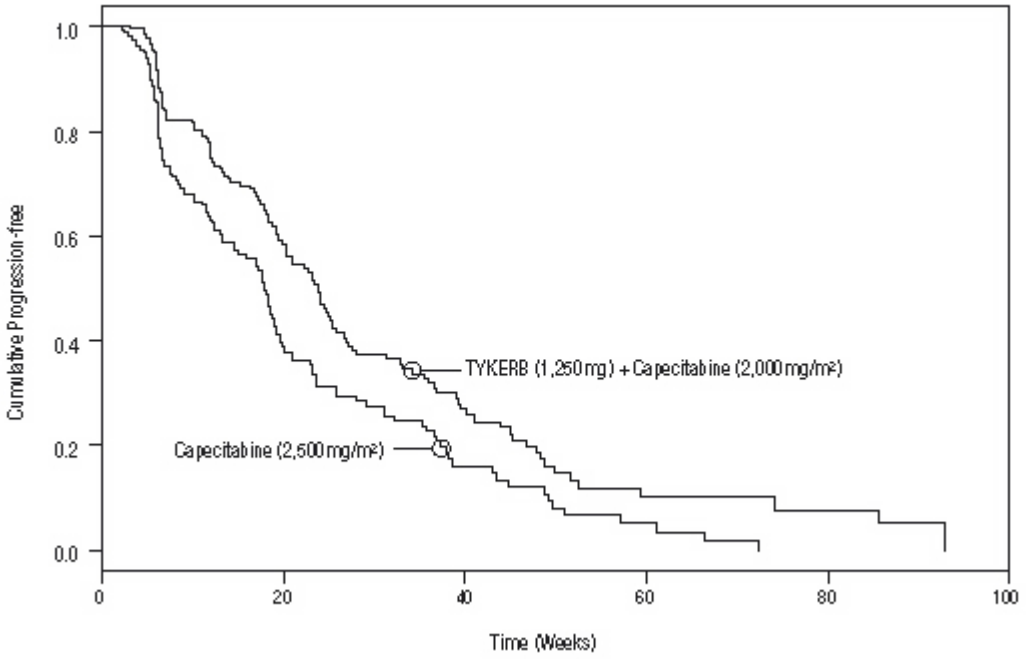


Figure 2. Kaplan-Meier Estimates for Investigator Assessment Time to Progression



At the time of above efficacy analysis, the overall survival data were not mature (32% events). However, based on the TTP results, the study was unblinded and patients receiving capecitabine alone were allowed to cross over to treatment with TYKERB plus capecitabine. The survival data were followed for an additional 2 years to be mature and the analysis is summarized in Table 6.

Table 6: Overall Survival Data

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day (N = 207)	**Capecitabine 2,500 mg/m^2/day (N = 201)**
Overall Survival		
Died	76%	82%
Median Overall Survival (weeks)	75.0	65.9
Hazard ratio, 95% CI (*P* value)	0.89 (0.71, 1.10) 0.276	

CI = confidence interval.

Clinical Studies Describing Limitation of Use: In two randomized trials, TYKERB-

based chemotherapy regimens have been shown to be less effective than trastuzumab-based chemotherapy regimens. The first randomized, open-label study compared the safety and efficacy of TYKERB in combination with capecitabine relative to trastuzumab in combination with capecitabine in women with HER2-positive metastatic breast cancer (N = 540). The study was stopped early based on the findings of a pre-planned interim analysis showing a low incidence of CNS events (primary endpoint) and superior efficacy of the trastuzumab plus capecitabine. The median progression-free survival was 6.6 months in the group receiving TYKERB in combination with capecitabine compared with 8.0 months in the group receiving the trastuzumab combination [HR = 1.30 (95% CI: 1.04, 1.64)]. Overall survival was analyzed when 26% of deaths occurred in the group receiving TYKERB in combination with capecitabine and 22% in the group receiving the trastuzumab combination [HR = 1.34 (95% CI: 0.95, 1.92)].

The second randomized, open-label study compared the safety and efficacy of taxane-based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line therapy in women with HER2–positive, metastatic breast cancer (N = 652). The study was stopped early based on findings from a pre-planned interim analysis. The median progression-free survival was 11.3 months in the trastuzumab combination treatment arm compared to 9.0 months in patients treated with TYKERB in the combination arm for the intent-to-treat population [HR = 1.37 (95% CI: 1.13, 1.65)].

14.2 Hormone Receptor Positive, HER2-Positive Metastatic Breast Cancer

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women with hormone receptor-positive (ER positive and/or PgR positive) metastatic breast cancer, who had not received prior therapy for metastatic disease, were randomly assigned to receive either TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH) ≥2 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2-negative and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective was to evaluate and compare progression-free survival (PFS) in the HER2-positive population. Progression-free survival was defined as the interval of time between date of randomization and the earlier date of first documented sign of disease progression or death due to any cause.

The baseline demographic and disease characteristics were balanced between the two treatment arms. The median age was 63 years and 45% were 65 years of age or older. Eighty-four percent (84%) of the patients were white. Approximately 50% of the HER2-positive population had prior adjuvant/neo-adjuvant chemotherapy and 56% had prior hormonal therapy. Only 2 patients had prior trastuzumab.

In the HER2-positive subgroup (n = 219), the addition of TYKERB to letrozole resulted in an improvement in PFS. In the HER2-negative subgroup, there was no improvement in PFS of the combination of TYKERB plus letrozole compared to the letrozole plus placebo. Overall

response rate (ORR) was also improved with the combination of TYKERB plus letrozole. The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor-positive, HER2-positive and HER2-negative subgroups are presented in Table 7 and Figure 3.

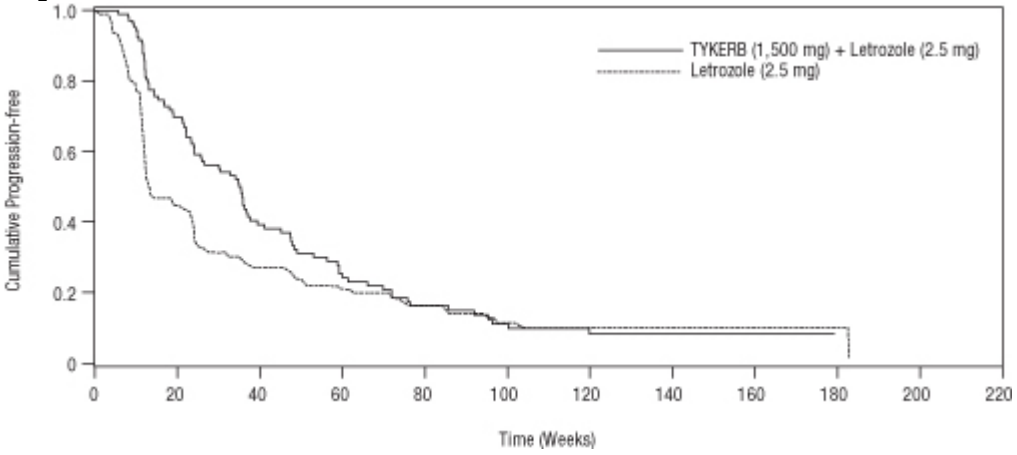
Table 7. Efficacy Results

	HER2-Positive Population		**HER2-Negative Population**	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	**Letrozole 2.5 mg/day**	**TYKERB 1500 mg/day + Letrozole 2.5 mg/day**	**Letrozole 2.5 mg/day**
	(N = 111)	**(N = 108)**	**(N = 478)**	**(N = 474)**
Median PFS[a], weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
Hazard Ratio (95% CI)	0.71 (0.53, 0.96)		0.90 (0.77, 1.05)	
***P* value**	0.019		0.188	
Response Rate (%) (95% CI)	27.9 (19.8, 37.2)	14.8 (8.7, 22.9)	32.6 (28.4, 37.0)	31.6 (27.5, 36.0)

PFS = progression-free survival; CI = confidence interval.

[a] Kaplan-Meier estimate.

Figure 3. Kaplan-Meier Estimates for Progression-Free Survival for the HER2-Positive Population



16 HOW SUPPLIED/STORAGE AND HANDLING

The 250 mg tablets of TYKERB are oval, biconvex, orange, and film-coated with GS XJG debossed on one side and are available in:

Bottles of 150 tablets: NDC 0173-0752-00

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

17.1 Information for Patients

Patients should be informed of the following:

- TYKERB has been reported to decrease left ventricular ejection fraction which may result in shortness of breath, palpitations, and/or fatigue. Patients should inform their physician if they develop these symptoms while taking TYKERB.
- TYKERB often causes diarrhea which may be severe in some cases. Patients should be told how to manage and/or prevent diarrhea and to inform their physician immediately if there is any change in bowel patterns or severe diarrhea occurs during treatment with TYKERB.
- TYKERB may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products.
- TYKERB may interact with grapefruit. Patients should not take TYKERB with grapefruit products.
- TYKERB should be taken at least one hour before or one hour after a meal, in contrast to capecitabine which should be taken with food or within 30 minutes after food.
- The dose of TYKERB should be taken once daily. Dividing the daily dose is not recommended.

TYKERB is a registered trademark of the GlaxoSmithKline group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

TKB:XXPI

PHARMACIST - DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TYKERB® (TIE-curb)
(lapatinib)
tablets

Read this leaflet before you start taking TYKERB and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is TYKERB?

TYKERB is used with the medicine capecitabine for the treatment of people with advanced or metastatic breast cancer that is HER2-positive (tumors that produce large amounts of a protein called human epidermal growth factor receptor-2), and who have already had certain other breast cancer treatments.

TYKERB is also used with a type of medicine called letrozole for the treatment of postmenopausal women with hormone receptor-positive, HER2-positive metastatic breast cancer for whom hormonal therapy is indicated.

It is not known if TYKERB is safe and effective in children.

Who should not take TYKERB?

Do not take TYKERB if you are allergic to any of the ingredients in TYKERB. See the end of this leaflet for a complete list of ingredients in TYKERB.

What should I tell my doctor before taking TYKERB?

Before you take TYKERB, tell your doctor if you:

- have heart problems.
- have liver problems. You may need a lower dose of TYKERB.
- have any other medical conditions
- are pregnant or plan to become pregnant. TYKERB can harm your unborn baby. You should not become pregnant while taking TYKERB. Tell your doctor right away if you become pregnant during treatment with TYKERB.
- are breastfeeding or plan to breastfeed. It is not known if TYKERB passes into your breast milk. You and your doctor should decide if you will take TYKERB or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TYKERB may affect the way other medicines work, and other medicines may affect the way TYKERB works.

Especially tell your doctor if you take:

- antibiotics and anti-fungal medicines (used to treat infections)
- HIV medicines
- medicines used to treat seizures
- medicines used to treat heart problems or high blood pressure
- antidepressants
- medicines that reduce stomach acid (antacids)
- St. John's wort

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine. Do not take other medicines during treatment with TYKERB without first talking with your doctor.

How should I take TYKERB?

- Take TYKERB exactly as your doctor tells you to take it. Your doctor may change your dose of TYKERB if needed.
  - For people with advanced or metastatic breast cancer, TYKERB and capecitabine are taken in 21-day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by mouth all at once, **one time a day on days 1 to 21**.
  - Your doctor will tell you the dose of capecitabine you should take and when you should take it.
  - Take capecitabine with food or within 30 minutes after food.
  - For people with hormone receptor-positive, HER2-positive breast cancer, TYKERB and letrozole are taken **every day**. The usual dose of TYKERB is 1,500 mg (6 tablets) taken by mouth all at once, **one time a day**. Your doctor will tell you the dose of letrozole you should take and when you should take it.
- TYKERB should be taken at least 1 hour before, or at least 1 hour after a meal.
- Do not eat or drink grapefruit products during treatment with TYKERB.
- If you miss a dose of TYKERB, take your next dose at your regular time the next day.
- If you take too much TYKERB, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of TYKERB?

TYKERB may cause serious side effects, including:

- **heart problems,** including decreased pumping of blood from the heart and an abnormal heartbeat. Signs and symptoms of an abnormal heartbeat include:
  - feeling like your heart is pounding or racing
  - dizziness
  - tiredness
  - feeling lightheaded
  - shortness of breath

  Your doctor should check your heart function before you start taking TYKERB and during treatment.
- **liver problems.** Liver problems can be severe and deaths have happened. Signs and symptoms of liver problems include:
  - itching
  - yellowing of your skin or the white part of your eyes
  - dark urine
  - pain or discomfort in the right upper stomach area

  Your doctor should do blood tests to check your liver before you start taking TYKERB and during treatment.
- **diarrhea.** Diarrhea is common with TYKERB and may sometimes be severe. Severe diarrhea can cause loss of body fluid (dehydration) and some deaths have happened. Call your doctor right away if you have a change in bowel pattern or if you have severe diarrhea. Follow your doctor's instructions for what to do to help prevent or treat diarrhea.
- **lung problems.** Symptoms of a lung problem with TYKERB include a cough that will not go away or shortness of breath.

Call your doctor right away if you have any of the signs or symptoms of the serious side effects listed above.

Common side effects of TYKERB in combination with capecitabine or letrozole include:

- diarrhea
- red, painful hands and feet
- nausea
- rash
- vomiting
- tiredness or weakness
- mouth sores

- loss of appetite
- indigestion
- unusual hair loss or thinning
- nose bleeds
- headache
- dry skin
- itching
- nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TYKERB. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also get side effects from the other medicines taken with TYKERB. Talk to your doctor about possible side effects you may get during treatment.

How should I store TYKERB Tablets?

- Store TYKERB Tablets at room temperature between 68° and 77°F (20° and 25°C).
- Keep the container closed tightly.
- Do not keep medicine that is out of date or that you no longer need.

Keep TYKERB and all medicines out of the reach of children.

General information about TYKERB

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use TYKERB for a condition for which it was not prescribed. Do not give TYKERB to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about TYKERB. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about TYKERB that is written for health professionals.

For more information, call 1-888-825-5249 or go to www.tykerb.com.

What are the ingredients in TYKERB?

Active ingredient: Lapatinib.

Inactive ingredients: Tablet Core: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat: FD&C yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

TYKERB is a registered trademark of the GlaxoSmithKline group of companies.

GlaxoSmithKline
Research Triangle Park, NC 27709

Revised: October 2013
TKB:XXPIL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022059Orig1s017

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 022059
Tykerb® (lapatinib) 250 mg Tablet

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Lyle Canida
Barbara Fuller
Lashawn Griffiths
Anthony J. Murgo
Michael Pacanowski
Marybeth Toscano

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022059Orig1s017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	022059
Submission Date	12/16/2012
Applicant Name	GlaxoSmithKline
Generic Name	Lapatinib
Proposed Indication	Metastatic breast cancer
Primary Reviewer	Lyle Canida, Pharm.D., M.S.
Secondary Reviewer	Rosane Charlab Orbach, Ph.D.
Associate Director	Mike Pacanowski, Pharm.D., M.P.H.

1 Background

Lapatinib is an oral dual EGFR/HER2 tyrosine kinase inhibitor (TKI) approved for HER2-positive advanced or metastatic breast cancer (MBC). As noted in the current Boxed Warning, lapatinib has been associated with isolated hepatic enzyme elevations as well as severe, life-threatening hepatotoxicity during the clinical trial and post-approval experience. The applicant conducted pharmacogenetic association studies in an attempt to identify potential genetic markers underlying hepatotoxicity risk. Four genetic markers were associated with lapatinib-induced liver adverse events: three common alleles in the Human Leukocytic Antigen (HLA) region (HLA-DRB1*07:01, -DQA1*02:01 and -DQB1*02:02) and a single nucleotide polymorphism (rs12153855) in an adjacent gene, tenascin XB (TNXB). The results of these analyses were previously submitted to FDA (03/2009) and also published in the literature (PMID: 21245432). Based on the results of these analyses, the applicant has proposed labeling revisions to describe the potential for an increased risk of hepatotoxicity in lapatinib-treated patients carrying specific HLA alleles. The purpose of this review is to verify the association between the HLA biomarkers and increased risk of hepatotoxicity and the adequacy of labeling regarding the association.

2 Submission Contents Related to Genomics

The labeling revision submitted by the applicant is as follows:

(b) (4)

The labeling revision proposed by the applicant is supported by retrospective analyses of several Phase 1 to 3 trials. Analyses were performed in two stages: an exploratory discovery stage and a confirmatory stage. The exploratory analysis was a genome-wide association study using pooled data from twelve Phase 1 to Phase 3 studies that evaluated lapatinib as monotherapy or in combination with chemotherapy in MBC patients (total n=901). Confirmatory analyses were based on a single phase 3 trial in MBC (EGF30008; n=371). The reported associations with the HLA markers were then replicated in an independent adjuvant breast cancer trial (EGF 105485/TEACH; n=1194).

In support of the labeling supplement, the applicant submitted a pharmacogenetic study report related to TEACH analysis entitled "EGF114471 Pharmacogenetic substudy for the determination of associations and predictive values of four MHC genetic variants for lapatinib-associated ALT elevation and hepatotoxicity using patients from EGF105485 (TEACH): A prospective validation of confirmed liver safety biomarkers HLA-DQA1*02:01 and DRB1*07:01 (18JUL2012)", and the associated datasets (Table 2).

Table 2: Datasets submitted for statistical analysis

Dataset	Description of dataset
conmeds.xpt	Concomitant medications
ctx.xpt	Anti-Cancer Therapy
demog.xpt	Demography
dilipgx.xpt	PGx DILI Case Control Statuses
genepoly.xpt	Polymorphism to Gene Mapping Data
genotype.xpt	Genotyping Data
lab.xpt	Laboratory Data
medhist.xpt	Medical History
oncsurv.xpt	Oncology Survival Analysis Dataset
pop.xpt	Population Flags
rucam.xpt	Liver Events RUCAM Scoring

Source: EDR

Reviewer comment: The sponsor did not submit data from the initial genome-wide association study.

TEACH was a randomized phase 3, double-blind, multicenter adjuvant study of lapatinib 1500 mg daily vs. placebo in women with early stage HER2 overexpressing breast cancer. In this analysis, the applicant genotyped the four MHC markers in the study: rs12153855 in the TNXB gene, HLA-DRB1*07:01, HLA-DQA1*02:01, and HLA-DQB1*02:02. 4 digit HLA genotyping was performed using the LABType SSO Typing test and genotyping for TNXB rs12152855 was performed using the Illumina Human 1M-DUO beadchip array.

3 Key Questions and Summary of Findings

3.1 Are the HLA variant alleles DQA1*02:01 and DRB1*07:01 associated with an increased risk of hepatotoxicity in patients treated with lapatinib?

*Yes, in the applicant's pharmacogenetic substudy, the odds ratio (OR) for carriers of the alleles DQA1*02:01 or DRB1*07:01 vs. non-carriers in strictly defined cases of ALT elevation >3 times upper limit of normal range (>3 x ULN) was 19.95 (CI 8.12 – 49.02). Cumulative incidence of ALT elevation >3 x ULN continued to increase during the study in carriers of the HLA variants while non-carrier cases were similar to rates in the placebo arm.*

3.1.1 Primary analyses

The pharmacogenetic substudy (EGF11471) submitted in support of this supplement was conducted using DNA and safety data collected from subjects enrolled in EGF105485 (TEACH). Germline DNA was collected at baseline from 2453 subjects (78%) of which 1194 were in the lapatinib arm and 1259 were in the placebo arm; 846 subjects (71%) in the lapatinib arm had clinical liver chemistry data available.

For measures of association, the applicant defined cases and controls as follows:

- *Strict ALT cases:* a lapatinib-treated subject with a baseline ALT ≤1 x ULN and one or more on treatment ALT elevation >3 x ULN during the study course.
- *Strict ALT controls:* subjects exposed to lapatinib for at least 13 weeks with baseline and all on treatment ALT measurements within normal range (≤ 1x ULN). Previous analyses by the applicant of lapatinib breast cancer trials showed by thirteen weeks approximately 50% of ALT cases had their first ALT elevation of >3 x ULN. However, ALT elevations >3 x ULN may occur later than 13 weeks past treatment initiation.
- *Broad ALT cases:* lapatinib-treated subjects with one or more ALT >3 x ULN during course of treatment, and
- *Broad non-cases:* all subjects with at least one laboratory measurement and not a broad ALT case. These additional definitions were used for determination of clinical utility.

The distribution of cases and controls by treatment arm and genotype availability in TEACH can be seen in table 3 below.

Table 3. Strictly defined cases/controls by treatment arm and genotype availability

	Lapatinib with genotype data (N=1194)	**Lapatinib with no genotype data (N=378)**	**Placebo with genotype data (N=1259)**	**Placebo with no genotype data (N=315)**
Strictly defined cases				
Case	34 (2.8)	6 (1.6%)	5 (0.4%)	1 (0.3%)
Control	812 (68.0%)	228 (60.3%)	1076 (85.5%)	245 (77.8%)
Neither	260 (21.8%)	87 (23.0%)	150 (11.9%)	39 (12.4%)
Missing Data	88 (7.4%)	57 (15.1%)	28 (2.2%)	30 (9.5%)
Broadly defined cases				
Case	37 (3.1%)	6 (1.6%)	6 (0.5%)	4 (1.3%)
Non-case	1071 (89.7%)	317 (83.9%)	1228 (97.5%)	283 (89.8%)
Missing Data	86 (7.2%)	55 (14.6%)	25 (2.0%)	28 (8.9%)

Source: EGF114471 Table 1.

Demographic and baseline characteristics data provided by the applicant included race, ethnicity, child-bearing potential, age, and BMI (calculated from height and weight). Differences between

subjects with genotype data and those without were balanced except for self-reported racial/ethnic background (Table 4). The study population was predominantly white.

Table 4. Demographics and baseline characteristics: genotyped vs. not genotyped

	Not Genotyped	Genotyped
	N (%)	N (%)
Total	**704 (22.4)**	**2443 (77.6)**
Race		
African American/African Heritage	35 (5.0)	80 (3.3)
American Indian or Alaskan Native	29 (4.1)	103 (4.2)
Asian - Central/South Asian Heritage	7 (1.0)	32 (1.3)
Asian - East Asian Heritage	112 (15.9)	353 (14.4)
Asian - Japanese Heritage	1 (0.1)	1 (0.0)
Asian - South East Asian Heritage	41 (5.8)	121 (5.0)
Native Hawaiian or Other Pacific Islander	1 (0.1)	15 (0.6)
White - Arabic/North African Heritage	8 (1.1)	5 (0.2)
White - Caucasian/European Heritage	470 (66.8)	1733 (70.9)
Ethnicity		
Hispanic or Latino	173 (24.6)	253 (10.4)
Not Hispanic or Latino	531 (75.4)	2190 (89.6)
Child Bearing Potential		
Post-menopausal	492 (69.9)	1634 (67.3)
Potentially able to bear	162 (23.0)	606 (24.8)
Sterile (of child-bearing age)	50 (7.1)	203 (8.3)
	Mean (95%CI)	**Mean (95%CI)**
Age	51.8 (51.1, 52.5)	52.0 (51.6, 52.4)
BMI	27.0 (26.6, 27.4)	26.8 (26.6, 27.1)

Source: Reviewer's analysis

Strict ALT cases and controls within the genetic substudy were not balanced with respect to age ($p<0.05$) although other factors did not differ significantly (Table 5).

Table 5. Demographics and baseline characteristics: strict ALT cases vs. controls

	Cases	Controls
	N (%)	N (%)
Total	**33 (4.0)**	**796 (96.0)**
Race		
African American/African Heritage	0 (0.0)	22 (2.8)
American Indian or Alaskan Native	2 (6.1)	28 (3.5)
Asian - Central/South Asian Heritage	0 (0.0)	12 (1.5)
Asian - East Asian Heritage	1 (3.0)	138 (17.3)
Asian - Japanese Heritage	0 (0.0)	1 (0.1)
Asian - South East Asian Heritage	1 (3.0)	35 (4.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	3 (0.4)
White - Caucasian/European Heritage	29 (87.9)	557 (70.0)
Ethnicity		
Hispanic or Latino	7 (21.2)	66 (8.3)
Not Hispanic or Latino	26 (78.8)	730 (91.7)

Table 5. Demographics and baseline characteristics: strict ALT cases vs. controls

Child Bearing Potential		
Post-menopausal	27 (81.8)	505 (63.4)
Potentially able to bear	5 (15.2)	217 (27.3)
Sterile (of child-bearing age)	1 (3.0)	74 (9.3)
	Mean (95%CI)	**Mean (95%CI)**
Age	56.9 (53.8, 60.1)	51.2 (50.5, 51.9)
BMI	27.0 (25.5, 28.5)	26.5 (26.2, 26.9)

Source: reviewer's analysis

The prevalence of the two HLA variants proposed for inclusion in labeling – HLA-DQA1*02:01 and -DRB1*07:01 – in EGF105485 (TEACH) was 25% in White/Caucasians (n=1735) and 15% in East Asians (n=353), which were the predominant races represented in the study. Demographic and clinical characteristics did not differ significantly by HLA genotype.

The applicant performed logistic regression to estimate odds ratios and confidence intervals for the association of the HLA variants with case-control status. Covariates for the regression were screened using backward selection. Categorical analyses were compared with Pearson's chi-square and quantitative analyses were compared with Wilcoxon rank sum statistic. Cox proportional hazards model was used for time to event analysis for carriers vs. non-carriers.

Odds ratios and corresponding p-values for strictly defined cases/controls between carriers and non-carriers by genotype category are shown in table 6 below. The odds ratio for the carriers of the two variants HLA-DQA1*02:01 and - DRB1*07:01vs non-carriers was approximately 20 with a greater frequency of strict ALT cases in the carrier group. The applicant reports that adjusting for age and race had a minor influence on the magnitude of marker effects and odds ratios. As such, unadjusted odds ratios are reported. Pair-wise conditional regression found TNXB rs12153855 and HLA-DQB1*02:02 non-significant when either HLA-DQA1*02:01 or -DRB1*07:01 were included as covariates, suggesting these two latter MHC markers are the primary association with strict ALT cases.

Table 6. Strictly defined cases/controls by genotype among lapatinib-treated subjects

Marker	**Genotype category**	**Cases N (%)**	**Controls N (%)**	**OR (unadjusted) (95% CI)**	**p-value**
HLA-DRB1*07:01	Carrier Non-carrier Total	17 (50.0) 17 (50.0) 34	153 (18.9) 655 (81.1) 808	19.98 (8.13 – 49.10)	1.4e-14
HLA-DQA1*02:01	Carrier Non-carrier Total	17 (50.0) 17 (50.0) 34	153 (19.0) 654 (81.0) 807	19.95 (8.12 – 49.02)	1.5e-14

Source: EGF114471 Table 2.

Odds ratios and predictive utility estimates (sensitivity, specificity, positive and negative predictive values [PPV, NPV] for HLA-DRB1*07:01 are summarized below according to peak ALT measurement during the study period (Table 7). Odds ratio for >10x ULN were not calculated because all cases were carriers of the variant.

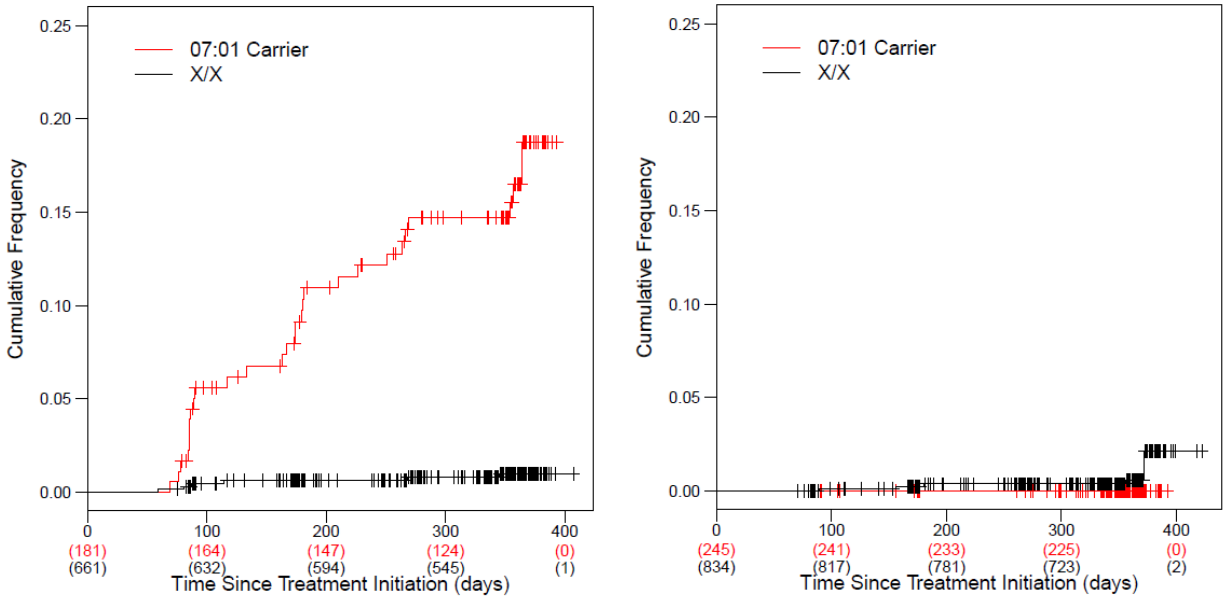
Table 7. Performance metrics for HLA-DRB1*07:01 variant in broadly defined cases and controls

ALT range	Carrier status	Cases N	Non-cases N	OR (unadjusted) (95% CI)	Overall case risk	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
>3xULN	Carrier Non-carrier	29 8	218 848	14.12 (6.36, 31.32)	3.1%	78.4 (61.8, 90.2)	79.6 (77.0, 82.0)	11.7 (8.0, 16.4)	99.1 (98.2, 99.6)
>5xULN	Carrier Non-carrier	19 4	228 852	17.77 (5.99, 52.75)	1.9%	82.6 (61.2, 95.1)	78.9 (76.4, 81.3)	7.7 (4.7, 11.8)	99.5 (98.8, 99.9)
>10xULN	Carrier Non-carrier	8 0	239 856		0.67%	100.0 (63.1, 100.0)	78.2 (75.6, 80.6)	3.2 (1.4, 6.3)	100.0 (99.6, 100.0)

Source: EGF114471 Table 3, study report results.

The cumulative incidence of ALT>3 x ULN in HLA carriers increased during the duration of the study. Subjects were censored at time of last laboratory measurement if their ALT remained <3 x ULN on treatment or up to 30 days post treatment. Figure 1 below shows the cumulative incidence of ALT >3 x ULN in strict cases and controls by HLA-DRB1*07:01 allele carrier status.

Figure 1. Cumulative incidence of ALT >3 x ULN in strict cases and controls by HLA-DRB1*07:01 carrier status in lapatinib (left) and placebo (right) arms



Source: EGF114471 Figure 2.

Reviewer comment: Incidence of ALT >3 x ULN can occur at any time during lapatinib therapy in these patients who carry the variant HLA alleles.

The analyses reported by the sponsor were reproduced with minor negligible differences noted in the point estimates because there were three fewer controls in each of the ALT severity levels (>3, >5, >10 x ULN) in the datasets submitted by the applicant.

3.1.2 Additional analyses

Carrier status and frequencies by race and ethnicity for all genotyped subjects can be seen in

table 8 below. These frequencies are consistent with those reported in The Allele Frequency Database (http://alfred.med.yale.edu) and the Allele Frequency Net Database (AFND: http://www.allelefrequencies.net).

Table 8. HLA-DQA1*02:01 carrier status and frequency by race/ethnicity (all genotyped subjects)

	Carrier Status		
Race	**Carrier N**	**Non-carrier N**	**Carrier Frequency**
African American	13	67	0.16
Asian	105	520	0.17
White	430	1309	0.25
Total	548	1895	0.22
Ethnic group			
Hispanic or Latino	53	200	0.21
Not Hispanic or Latino	495	1695	0.23

Source: reviewer analysis

An additional analysis was performed to evaluate the effect of HLA genotype on hepatotoxicity risk across different racial/ethnic subgroups. It is difficult to make a conclusion due to the small numbers in the population subgroups (Table 9).

Table 9. Incidence of severe ALT (>5 x ULN) by race/ethnicity (lapatinib arm only)

	Incidence (%)	
Race	**Carrier**	**Non-carrier**
African American	0.0	0.0
Asian	2.1	0.0
White	9.3	0.7
Total	7.7	0.5
Ethnic group		
Hispanic or Latino	24.0	5.9
Not Hispanic or Latino	0.0	0.5

Source: reviewer analysis

Overall risk of liver injury stratified by ALT elevation and HLA-DRB1*07:01 carrier status for broadly defined lapatinib-treated subjects can be seen in Table 10 below. Odds ratio for >10 x ULN was not calculated because all cases were carriers of the variant. Numbers needed to screen (NNS) are shown for each level of severity risk. NNS were calculated by taking the inverse of the absolute risk reduction between overall case risk (table 7) and risk for non-carriers within each ALT severity range divided by the prevalence of positive carrier status.

Table 10. OR and risk for cases/non-cases by ALT range and carrier status

ALT range HLA-DRB1*07:01 carrier status		Cases	Non-cases	OR (unadjusted) (95% CI)	Risk %	NNS
>3 x ULN	Carrier	29	218	14.06	11.7	214
	Non-carrier	8	846	(6.34, 31.25)	0.94	
>5 x ULN	Carrier	19	228	17.7	7.7	319
	Non-carrier	4	850	(5.97, 52.63)	0.47	
>10 x ULN	Carrier	8	239	Not calculated	3.24	682
	Non-carrier	0	854		0.0	

Source: reviewer analysis

To determine if time to ALT elevation can predict severity of liver injury, a regression analysis of the severe ALT cases was performed. No clear trend in ALT levels over time was shown for the severe ALT cases (>5 x ULN) in this analysis (R-Square = 0.0007). ALT levels reached >5 x ULN at various time points throughout the study with high subject variability.

A strong correlation was observed in this study between the two alleles HLA-DRB1*07:01 and HLA-DQA1*02:01. It is difficult to isolate which HLA variant allele is causative. Two subjects were carriers of the *07:01 allele without the *02:01 allele and two subjects were carriers of the *02:01 allele without the *07:01 allele. All other carriers in the study were positive for both alleles (N=546).

A search of allelefrequencies.net for each of the HLA allele and haplotype frequencies was performed. Only populations reporting both HLA alleles and haplotype frequencies within the same sample and with N ≥ 100 were included. While there was a high correlation between HLA variants in the submitted pharmacogenetic study, reported frequencies from allelfrequencies.net suggests variability in linkage disequilibrium across races and geographic regions (Table 11).

Table 11. Selected HLA allele/haplotype frequencies by race group

	Median allele frequency % (range)			
Race	**HLA-DRB1*07:01**	**HLA-DQA1*02:01**	**Haplotype *07:01 + *02:01**	**% Correlation (Range)**
Black	6.6	5.1	4.9	75 - 96
Asian	18.8 (5.7 – 25.7)	18.7 (5.6 – 27.6)	13.4 (4.4 – 19.9)	43 - 98
White	13.3 (9 – 25.8)	13.3 (8.8 – 26)	10.5 (6.6 – 20.6)	37 - 100

Source: allelefrequencies.net

Reviewer comment: An insufficient number of Asian subjects were available for analysis to assess which allele was driving the association.

4 Summary and Conclusions

The HLA variant alleles DQA1*02:01 and DRB1*07:01 appear to be associated with an increased risk of hepatotoxicity in patients treated with lapatinib. The overall study population risk for severe liver injury (Grade 3) was 1.9%. However, in carriers of the HLA-DRB1*07:01 variant the incidence of severe liver injury was 7.7%.

The association between HLA-DQA1*02:01 and -DRB1*07:01 and lapatinib-induced severe liver injury was originally discovered in a meta-analysis of lapatinib trials, and has been replicated in substudies of two independent clinical trials. The effect is large with odds ratios of approximately 20 (lower bound of 95%CI >8) for carriage of HLA-DQA1*02:01 and -DRB1*07:01 (incidence 7.7%) vs. non-carriers (incidence 0.47%). The association is consistent across various case definitions, with increasing sensitivity and specificity with more strict case definitions.

The substudy population did not differ significantly from the overall trial population in terms of demographic or clinical characteristics. Adjustment for potential confounders such as age and race/ethnicity, did not significantly affect point estimates for the relationship between HLA status and ALT changes. Carriage of these variants is common in the population, but differs by race/ethnicity (e.g., rare in Japanese). The majority of the population was White, and too few subjects were available within various racial/ethnic groups to evaluate the consistency of the association across these subgroups.

Many TKIs are known to cause hepatic injury. Lapatinib, pazopanib, ponatinib, regorafenib, sunitinib) have Boxed Warnings related to hepatotoxicity. Proposed mechanisms for hepatic adverse events vary among the TKIs. Lapatinib is the only TKI associated with a hepatotoxic reaction with a documented immunologic basis (given these data); other mechanisms associated with hepatotoxicity include autoimmunity, transport inhibition or direct cytotoxicity (PMID: 23556451).

From the reviewer's perspective, patients do not need to be routinely screened for these HLA alleles prior to administering lapatinib assuming the medical officer's concur that the risks are manageable through routine liver function monitoring. Liver function should be monitored routinely during lapatinib therapy as recommended in the labeling, with any reaction managed individually according to risk/benefit.

5 Recommendations

From the perspective of the Genomics and Targeted Therapy Group, the pharmacogenetic substudy results support the labeling revisions to include the information regarding the increase in risk associated with the HLA-DQA1*02:01 or -DRB1*07:01 variant alleles. Specific labeling recommendations are provided below.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

The applicant's proposed labeling changes are shown below in underline or ~~strikethrough~~. The reviewer's proposed changes are noted by underline or ~~strikethrough~~.

12 Clinical Pharmacology

…

12.5 Pharmacogenomics

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of patients overall; the incidence of severe liver injury among DQA1*02:01 or DRBI*07:01 allele carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately 15 to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese populations. Liver function should be monitored in all patients receiving therapy (b) (4) with TYKERB regardless of genotype.

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/s/

LYLE CANIDA
10/17/2013

ROSANE CHARLAB ORBACH
10/17/2013

MICHAEL A PACANOWSKI
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022059Orig1s017

OTHER REVIEW(S)

Division of Oncology Products 1
REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022059/SE8 - 017
Name of Drug: Tykerb® (lapatinib)
Applicant: SmithKline Beecham (Cork) Ltd., Ireland d/b/a GlaxoSmithKline

Labeling Reviewed

Submission Date: December 19, 2012
Receipt Date: December 19, 2012

1. BACKGROUND AND SUMMARY DESCRIPTION:

NDA 022059 is approved for the use of Tykerb® (lapatinib), a 250 mg kinase inhibitor tablet to treat HER-2 positive breast cancer patients.

SE8 - 017 provides for the following proposed revision to the package insert:

- Change to the package insert include increased risk of hepatotoxicity of Tykerb® in persons with HLA risk alleles based on pharmacogenetics data.

This supplement was reviewed by Lyle Canida, pharmacogenomics reviewer (See review signed on October 18, 2013). Internal labeling meetings were held September 4 and September 23, 2013, to review the sponsor's proposed label. Please see the attached labeling with review comments.

2. RECOMMENDATIONS

This supplement can be approved based on:

1. Pharmacogenomics review dated October 18, 2013.
2. Internal labeling meetings on September 4 and September 23, 2013 where clinical, pharmacogenomics, and division management attended.

{See appended electronic signature page}
Rajesh Venugopal
Regulatory Project Manager

Christy Cottrell
Chief, Project Management Staff

REVIEW

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/s/

RAJESH VENUGOPAL
10/21/2013

CHRISTY L COTTRELL
10/21/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 15, 2013
To:	Anthony Murgo, MD Acting Division Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TYKERB (lapatinib)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 22-059
Supplement Number:	S-016 S-017
Applicant:	GlaxoSmithKline

1 INTRODUCTION

On December 18, 2012 GlaxoSmithKline (GSK) submitted for the Agency's review a Prior Approval Supplement (S-016) to their New Drug Application (NDA) 22-059 for TYKERB (lapatinib). This labeling supplement provides proposed revisions to the indication statement for lapatinib given in combination with capecitabine. On December 19, 2012 GSK submitted Prior Approval Supplement S-017 to NDA 22-059 for TYKERB (lapatinib) in which GSK proposed revisions to the Prescribing Information (PI) to include information of the increased risk of hepatotoxicity in patients with HLA risk alleles.

TYKERB (lapatinib) was originally approved on March 13, 2007 and is indicated in combination with:

- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, ataxane, and trastuzumab.
- letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 1 (DOP1) on October 9, 2013 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for TYKERB (lapatinib) tablets.

2 MATERIAL REVIEWED

- Draft TYKERB (lapatinib) PPI received on December 18, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on October 9, 2013.
- Draft TYKERB (lapatinib) Prescribing Information (PI) received by DMPP on October 9, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
10/15/2013

BARBARA A FULLER
10/15/2013

LASHAWN M GRIFFITHS
10/15/2013

MEMORANDUM
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

******Pre-decisional Agency Information******

Memorandum

Date: October 11, 2013

To: Rajesh Venugopal, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft product labeling for Tykerb (lapatinib)
NDA 022059, S16, 17

In response to your consult request dated July 29, 2013, OPDP has reviewed the proposed product labeling (PI) for Tykerb efficacy supplements S 16 and 17. Specifically, OPDP has reviewed the Highlights and Sections 1, 12.5, 14.1, and the Patient Information, and has no comments.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

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/s/

MARYBETH TOSCANO
10/11/2013