DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Jean-Pierre Garnier, Ph.D.
Chief Executive Officer
GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Triangle Research Park, NC 27709-3398

RE: NDA # 22-059
TYKERB (lapatinib) Tablets
MACMIS #15851

WARNING LETTER

Dear Dr. Garnier:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed three Dear Healthcare Practitioner letters (P4 Healthcare Dear Dr. Letters - E-mail [TKB133R0], Dear Dr. Letter M.D. Alert [TKB131R0], and Tykerb Announcement - Dear Oncology Nurse Direct Mail Letter [TKB130R0]) for TYKERB (lapatinib) Tablets (Tykerb) submitted by GlaxoSmithKline (GSK) under cover of Form FDA 2253. These letters, which were part of the launch campaign for Tykerb, are misleading in that they omit and minimize the most serious and important risk information for Tykerb and selectively present efficacy information for Tykerb, thereby overstating the efficacy of the drug. Therefore, these promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) and 321(n); *Cf* 21 CFR 202.1(e)(5)(i); (iii), and (e)(6)(i). We are particularly concerned that these materials, which were disseminated to healthcare professionals during the product's launch and formed the basis of their first impressions of the drug, suggest to healthcare professionals that Tykerb is safer and more effective than has been demonstrated.

Background

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI)[1] for Tykerb:

> 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.

[1] These references are to the PI dated March 2007. We note that a new version of the PI was approved in August 2007; however, the March 2007 PI was the one in use at the time these pieces were disseminated.

The PI for Tykerb includes several risks associated with its use. It states (in pertinent part):

WARNINGS AND PRECAUTIONS

Decreased Left Ventricular Ejection Fraction
TYKERB has been reported to decrease LVEF. In the randomized clinical trial, the majority (>60%) of LVEF decreases occurred within the first 9 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 . . . . LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline below the institution's normal limits.

Patients with Severe Hepatic Impairment
If TYKERB is to be administered to patients with severe hepatic impairment, dose reduction should be considered.

Diarrhea
Diarrhea, including severe diarrhea, has been reported during treatment with TYKERB. Proactive management of diarrhea with anti-diarrheal agents is important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of therapy with TYKERB.

QT Prolongation
. . . Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc. . . . Hypokalemia or hypomagnesemia should be corrected prior to lapatinib administration. The prescriber should consider baseline and on-treatment electrocardiograms with QT measurement.

Pregnancy
Pregnancy Category D
TYKERB can cause fetal harm when administered to a pregnant woman. . . . 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.

ADVERSE REACTIONS

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 CTC v3) were diarrhea and palmar-plantar erythrodysesthesia.

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. . . . Among 198 patients who received lapatinib/capecitabine combination treatment, 3 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTC 3.0).

In addition, the Dosage and Administration section states the following regarding decreases in LVEF:

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 . . . and in patients with an LVEF that drops below the institution's lower limit of normal. Tykerb may be restarted at a reduced dose . . . if the LVEF recovers to normal and the patient is asymptomatic.

The Clinical Studies section of the PI presents efficacy results from both Independent and Investigator Assessments (in pertinent part):

	Independent Assessment		**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)**
Median TTP, weeks (25^{th}, 75^{th}, Percentile)	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 (95% CI) p value	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The promotional letters make prominent claims of effectiveness for the treatment of advanced or metastatic breast cancer but fail to present the most serious and important risk information from the PI. Specifically, the materials omit the warnings and precautions relating to pregnancy, patients with severe hepatic impairment and those who have or may develop QT prolongation. Furthermore, the materials fail to include any of the information from the Warnings and Precautions section regarding diarrhea, including the importance of proactive use of anti-diarrheal agents, the potential need for oral or intravenous electrolytes and fluids, and the potential need for interruption or discontinuation of Tykerb. We note that the letters list diarrhea as a commonly reported adverse event. However, this presentation does not reflect the seriousness of and treatment considerations for the diarrhea that can result from Tykerb therapy as stated in the Warnings and Precaution section of the PI (see background section).

Most important, the letters minimize the important risk of decreased left ventricular ejection fraction associated with Tykerb therapy, a risk sufficient to call for baseline and continued assessment of

cardiac function. Although the letters mention that LVEF was monitored during the trial (stating that "LVEF . . . was monitored during the study. Among 198 patients who received the TYKERB-capecitabine combination treatment, three experienced an asymptomatic (grade 2) decrease in LVEF and one experienced a symptomatic (grade 3) decrease in LVEF."), they fail to include additional important contextual information regarding the seriousness and necessary precautions associated with this risk from the Warnings and Precautions section of the PI. Specifically, this section states that "LVEF **should be evaluated in all patients prior to initiation of treatment with TYKERB**. . . . LVEF **should continue to be evaluated during treatment with TYKERB** . . . ." (emphasis added). The Warning and Precautions section also states that "Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function." Furthermore, as reflected in the Dosage and Administration section of the PI, Tykerb dosing may need to be suspended or reduced in the event of decreased LVEF. The promotional pieces fail to convey the importance of the effect of Tykerb on cardiac function.

Overstatement of Efficacy/Omission of Material Facts

The efficacy data collected during the clinical trial for Tykerb, including the primary endpoint of time to tumor progression (TTP), were evaluated by both a blinded independent review committee (IRC) and the investigators. Time to tumor progression does not measure the time to actual tumor progression, but rather the time to tumor assessment, and this distinction can make the quantification of actual tumor progression problematic, particularly when this measure is used in open label trials. The use of an IRC was meant to ameliorate some of the problems inherent with an open label trial. Per protocol, the blinded independent review was to be the basis of the primary analysis. The investigator assessments were the basis for treatment decisions, including discontinuation of treatment.

The results of these two distinct efficacy assessments differ due to several factors including, but not limited to, early termination of enrollment in the trial based on TTP data, differences in the data available to the two groups at the pre-defined interim analysis, differences in the time from last tumor assessment to data cut-off, and missing data[2]. For example, patients with disease progression as determined by the investigator discontinued study treatment. The treatment discontinuation marked the TTP for that patient. The IRC, however, was blinded to this event and instead took the time of death as the event date for the IRC assessment, falsely inflating the TTP in the IRC review. Additionally, although the pre-specified time intervals for tumor assessments were 42 and 84 days, the time from last tumor assessment to data cut-off was actually > 100 days in approximately 30% of patients in the independent assessment compared to only 13% of patients in the investigator assessment. While both assessments were statistically significant, the TTP data for the independent assessment was inflated because of the greater number of patients with later assessment dates. Because of these multiple issues, both analyses were required for the approval of Tykerb. Accordingly, the PI presents both analyses.

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. In these promotional materials, only the more favorable of the two distinct analyses of the effect of

[2] These differences are further detailed in the Medical Review conducted as part of the Approval Package for Tykerb (publicly available at http://www.fda.gov/cder/foi/nda/2007/022059s000_MedR_P1.pdf). See the Team Leader's review, pages 2-4, signed March 12, 2007, and the Clinical Review, pages 12-13, and 34, signed March 13, 2007.

Tykerb in breast cancer is shown. The letters present only the independent assessment results in any detail, claiming, "This approval was based on the pivotal Phase III trial of 399 patients which showed that the median time to disease progression as assessed by independent reviewers was 27.1 weeks on the combination of TYKERB and capecitabine versus 18.6 weeks on capecitabine alone. . . . The hazard ratio of 0.57 (95% CI: 0.43, 0.77, p = 0.00013) represents a 43 percent reduction in risk of progression for the patients on the combination arm." The letters, however, fail to present the investigator assessment for the same endpoints from the PI, which show a less favorable result. The hazard ratio for the investigator assessment of time to tumor progression is 0.72 (95% CI: 0.56, 0.92, p = 0.00762), a 28 percent risk reduction for tumor progression, considerably less than the 43 percent reduction reported by the independent assessment. Median time to progression as assessed by the investigators was 23.9 weeks on Tykerb versus 18.3 weeks on capecitabine alone, a difference of barely one month. The letters present only the more favorable analysis, thereby overstating the efficacy of the drug. Although the letters do contain the statement "Differences between treatment groups based on unblinded investigator assessments were smaller but continued to be clinically and statistically significant," this statement does not mitigate the misleading impression conveyed by the letters.

Conclusion and Requested Action

The Dear Healthcare Practitioner letters are misleading in that they omit and minimize important risk information for Tykerb and selectively present efficacy information for Tykerb, thereby overstating the efficacy of the drug. Therefore, these promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) and 321(n); *Cf* 21 CFR 202.1(e)(5)(i); (iii), and (e)(6)(i).

DDMAC requests that GlaxoSmithKline immediately cease the dissemination of violative promotional materials for Tykerb such as those described above. Please submit a written response to this letter on or before December 6, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Tykerb, such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID #15851 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Tykerb comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams
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