

**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**  
Warnings and Precautions, Severe Cutaneous Reactions (5.7) 12/2014

**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<sup>2</sup>/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)  
• Severe cutaneous reactions have been reported. Discontinue TYKERB if life-threatening reactions are suspected. (5.7)  
• Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.8)

**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: 12/2014

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: HEPATOTOXICITY**

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

## 6 **1 INDICATIONS AND USAGE**

7 TYKERB<sup>®</sup> is indicated in combination with:

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

11 Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation  
12 of treatment with TYKERB in combination with capecitabine.

- 13 • letrozole for the treatment of postmenopausal women with hormone receptor-positive  
14 metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is  
15 indicated.

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

## 18 **2 DOSAGE AND ADMINISTRATION**

### 19 **2.1 Recommended Dosing**

20 HER2-Positive Metastatic Breast Cancer: The recommended dose of TYKERB is  
21 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine  
22 2,000 mg/m<sup>2</sup>/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in  
23 a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a  
24 meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing  
25 the daily dose is not recommended [see *Clinical Pharmacology (12.3)*]. Capecitabine should be  
26 taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not  
27 double the dose the next day. Treatment should be continued until disease progression or  
28 unacceptable toxicity occurs.

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

### 35 **2.2 Dose Modification Guidelines**

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

37 ventricular ejection fraction (LVEF) that is Grade 2 or greater by National Cancer Institute  
38 Common Terminology Criteria for Adverse Events (NCI CTCAE v3) and in patients with an  
39 LVEF that drops below the institution's lower limit of normal [*see Warnings and Precautions*  
40 (5.1) and *Adverse Reactions* (6.1)]. TYKERB in combination with capecitabine may be restarted  
41 at a reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at a  
42 reduced dose of 1,250 mg/day after a minimum of 2 weeks if the LVEF recovers to normal and  
43 the patient is asymptomatic.

44 **Hepatic Impairment:** Patients with severe hepatic impairment (Child-Pugh Class C)  
45 should have their dose of TYKERB reduced. A dose reduction from 1,250 mg/day to  
46 750 mg/day (HER2-positive metastatic breast cancer indication) or from 1,500 mg/day to  
47 1,000 mg/day (hormone receptor-positive, HER2-positive breast cancer indication) in patients  
48 with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the  
49 normal range and should be considered. However, there are no clinical data with this dose  
50 adjustment in patients with severe hepatic impairment.

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

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

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

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

80 **Other Toxicities:** Discontinuation or interruption of dosing with TYKERB may be  
81 considered when patients develop  $\geq$ Grade 2 NCI CTCAE toxicity and can be restarted at the  
82 standard dose of 1,250 or 1,500 mg/day when the toxicity improves to Grade 1 or less. If the  
83 toxicity recurs, then TYKERB in combination with capecitabine should be restarted at a lower  
84 dose (1,000 mg/day) and in combination with letrozole should be restarted at a lower dose of  
85 1,250 mg/day.

86 **See manufacturer’s prescribing information for the coadministered product dosage**  
87 **adjustment guidelines in the event of toxicity and other relevant safety information or**  
88 **contraindications.**

### 89 **3 DOSAGE FORMS AND STRENGTHS**

90 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one  
91 side.

### 92 **4 CONTRAINDICATIONS**

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

### 95 **5 WARNINGS AND PRECAUTIONS**

#### 96 **5.1 Decreased Left Ventricular Ejection Fraction**

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

#### 105 **5.2 Hepatotoxicity**

106 Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin  
107 >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and  
108 postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.  
109 Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after  
110 initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase)  
111 should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as  
112 clinically indicated. If changes in liver function are severe, therapy with TYKERB should be  
113 discontinued and patients should not be retreated with TYKERB [*see Adverse Reactions (6.1)*].

114 **5.3 Patients With Severe Hepatic Impairment**

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

120 **5.4 Diarrhea**

121 Diarrhea has been reported during treatment with TYKERB [*see Adverse Reactions*  
122 *(6.1)*]. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs  
123 early during treatment with TYKERB, with almost half of those patients with diarrhea first  
124 experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib-induced diarrhea is  
125 usually low-grade, with severe diarrhea of NCI CTCAE Grades 3 and 4 occurring in <10% and  
126 <1% of patients, respectively. Early identification and intervention is critical for the optimal  
127 management of diarrhea. Patients should be instructed to report any change in bowel patterns  
128 immediately. Prompt treatment of diarrhea with anti-diarrheal agents (such as loperamide) after  
129 the first unformed stool is recommended. Severe cases of diarrhea may require administration of  
130 oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially  
131 if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and  
132 interruption or discontinuation of therapy with TYKERB [*see Dosage and Administration (2.2)*].

133 **5.5 Interstitial Lung Disease/Pneumonitis**

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

139 **5.6 QT Prolongation**

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

147 **5.7 Severe Cutaneous Reactions**

148 Severe cutaneous reactions have been reported with TYKERB. If life-threatening  
149 reactions such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal  
150 necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) are suspected,  
151 discontinue treatment with TYKERB.

152 **5.8 Use in Pregnancy**

153 TYKERB can cause fetal harm when administered to a pregnant woman. Based on

154 findings in animals, TYKERB is expected to result in adverse reproductive effects. Lapatinib  
155 administered to rats during organogenesis and through lactation led to death of offspring within  
156 the first 4 days after birth [see *Use in Specific Populations (8.1)*].

157       There are no adequate and well-controlled studies with TYKERB in pregnant women.  
158 Women should be advised not to become pregnant when taking TYKERB. If this drug is used  
159 during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be  
160 apprised of the potential hazard to the fetus.

## 161 **6 ADVERSE REACTIONS**

### 162 **6.1 Clinical Trials Experience**

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

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

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

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

177

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

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

179 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

180 <sup>b</sup> Grade 3 dermatitis acneiform was reported in <1% of patients in the group receiving  
181 TYKERB plus capecitabine.

182



183 **Table 2. Selected Laboratory Abnormalities**

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

184 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

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**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.

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

Reactions	TYKERB 1,500 mg/day + Letrozole 2.5 mg/day (N = 654)			Letrozole 2.5 mg/day (N = 624)		
	All Grades <sup>a</sup>	Grade 3	Grade 4	All Grades <sup>a</sup>	Grade 3	Grade 4
	%	%	%	%	%	%
<b>Gastrointestinal disorders</b>						
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
<b>Skin and subcutaneous tissue disorders</b>						
Rash <sup>b</sup>	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
<b>General disorders and administrative site conditions</b>						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
<b>Nervous system disorders</b>						
Headache	14	<1	0	13	<1	0
<b>Respiratory, thoracic, and mediastinal disorders</b>						
Epistaxis	11	<1	0	2	<1	0

196 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

197 <sup>b</sup> In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional  
 198 subjects in each treatment arm had rash under "Infections and infestations"; none were Grade  
 199 3 or 4.

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201 **Table 4. Selected Laboratory Abnormalities**

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

202 <sup>a</sup> National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

203  
 204 **Decreases in Left Ventricular Ejection Fraction:** Due to potential cardiac toxicity  
 205 with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week  
 206 intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular  
 207 cardiac function that are ≥Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac  
 208 ejection fraction relative to baseline which is below the institution's lower limit of normal.  
 209 Among 198 patients who received combination treatment with TYKERB/capecitabine, 3  
 210 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTCAE v3) [see  
 211 *Warnings and Precautions (5.1)*]. Among 654 patients who received combination treatment with  
 212 TYKERB/letrozole, 26 patients experienced Grade 1 or 2 and 6 patients had Grade 3 or 4 LVEF  
 213 adverse reactions.

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

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

## 219 **6.2 Postmarketing Experience**

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

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

226 **Skin and Subcutaneous Tissue Disorders:** Nail disorders including paronychia.

## 227 **7 DRUG INTERACTIONS**

### 228 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport** 229 **Systems**

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

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

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

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

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

## 248 **7.2 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

254 **Ketoconazole:** In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at  
255 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to  
256 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

257 **Carbamazepine:** In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at  
258 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to  
259 lapatinib was decreased approximately 72%.

## 260 **7.3 Drugs That Inhibit Drug Transport Systems**

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

## 264 **7.4 Acid-Reducing Agents**

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

# 269 **8 USE IN SPECIFIC POPULATIONS**

## 270 **8.1 Pregnancy**

271 **Pregnancy Category D** [*see Warnings and Precautions (5.8)*].

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

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

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

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

### 296 **8.3 Nursing Mothers**

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

### 301 **8.4 Pediatric Use**

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

### 303 **8.5 Geriatric Use**

304 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in  
305 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were  
306 75 years of age and older. Of the total number of hormone receptor-positive, HER2-positive  
307 metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole  
308 (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No  
309 overall differences in safety or effectiveness were observed between elderly subjects and  
310 younger subjects, and other reported clinical experience has not identified differences in  
311 responses between the elderly and younger patients, but greater sensitivity of some older  
312 individuals cannot be ruled out.

313 **8.6 Renal Impairment**

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

319 **8.7 Hepatic Impairment**

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

330 **10 OVERDOSAGE**

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

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

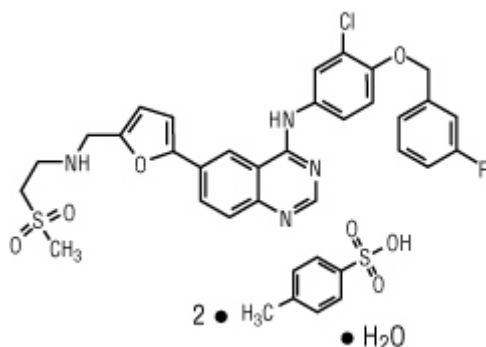
341 Because lapatinib is not significantly renally excreted and is highly bound to plasma  
342 proteins, hemodialysis would not be expected to be an effective method to enhance the  
343 elimination of lapatinib.

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

345 **11 DESCRIPTION**

346 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase  
347 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-  
348 chloro-4-{{(3-fluorophenyl)methyl}oxy}phenyl)-6-[5-({[2-  
349 (methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-  
350 methylbenzenesulfonate) monohydrate. It has the molecular formula C<sub>29</sub>H<sub>26</sub>ClFN<sub>4</sub>O<sub>4</sub>S  
351 (C<sub>7</sub>H<sub>8</sub>O<sub>3</sub>S)<sub>2</sub> H<sub>2</sub>O and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the

352 following chemical structure:



353

354 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is  
355 0.001 mg/mL at 25°C.

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

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

## 362 12 CLINICAL PHARMACOLOGY

### 363 12.1 Mechanism of Action

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

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

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

### 379 12.3 Pharmacokinetics

380 **Absorption:** Absorption following oral administration of TYKERB is incomplete and  
381 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to  
382 1.5 hours). Peak plasma concentrations ( $C_{max}$ ) of lapatinib are achieved approximately 4 hours

383 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to  
384 7 days, indicating an effective half-life of 24 hours.

385 At the dose of 1,250 mg daily, steady-state geometric mean (95% confidence interval)  
386 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  
387 56 mcg.h/mL).

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

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

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

399 **Metabolism:** Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and  
400 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated  
401 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or  
402 10% of lapatinib concentration in plasma.

403 **Elimination:** At clinical doses, the terminal phase half-life following a single dose was  
404 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

405 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with  
406 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of  
407 27% (range 3% to 67%) of an oral dose.

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

#### 410 **12.4 QT Prolongation**

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

#### 416 **12.5 Pharmacogenomics**

417 The HLA alleles DQA1\*02:01 and DRB1\*07:01 were associated with hepatotoxicity  
418 reactions in a genetic substudy of a monotherapy trial with TYKERB (n = 1,194). Severe liver  
419 injury (ALT >5 times the upper limit of normal, NCI CTCAE Grade 3) occurred in 2% of  
420 patients overall; the incidence of severe liver injury among DQA1\*02:01 or DRBI\*07:01 allele  
421 carriers was 8% versus 0.5% in non-carriers. These HLA alleles are present in approximately  
422 15% to 25% of Caucasian, Asian, African, and Hispanic populations and 1% in Japanese



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

## 425 **13 NONCLINICAL TOXICOLOGY**

### 426 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

427 Two-year carcinogenicity studies with lapatinib are ongoing.

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

433 There were no effects on male or female rat mating or fertility at doses up to  
434 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times  
435 the expected human clinical exposure based on AUC following 1,250-mg dose of lapatinib plus  
436 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,  
437 when female rats were given oral doses of lapatinib during breeding and through the first 6 days  
438 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and  
439 in the fetal body weights at  $\geq 60$  mg/kg/day (approximately 6.4 times and 3.3 times the expected  
440 human clinical exposure based on AUC following 1,250-mg dose of lapatinib plus capecitabine,  
441 respectively).

## 442 **14 CLINICAL STUDIES**

### 443 **14.1 HER2-Positive Metastatic Breast Cancer**

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

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

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

462

463 **Table 5. Efficacy Results**

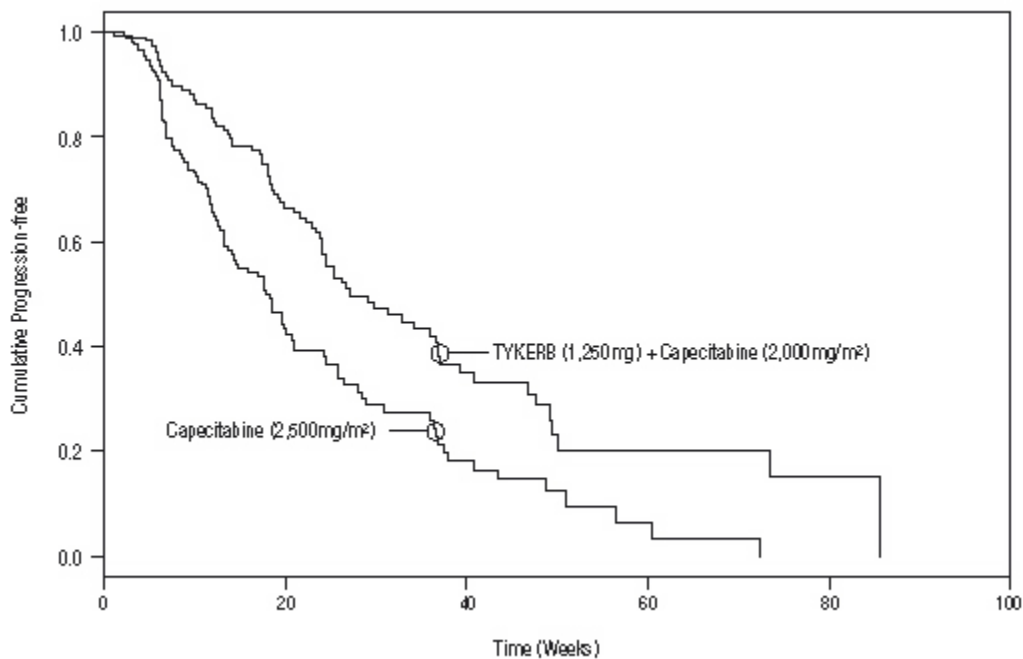
	Independent Assessment <sup>a</sup>		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m <sup>2</sup> /day	Capecitabine 2,500 mg/m <sup>2</sup> /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m <sup>2</sup> /day	Capecitabine 2,500 mg/m <sup>2</sup> /day
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
<b>Number of TTP events</b>	82	102	121	126
<b>Median TTP, weeks</b> (25 <sup>th</sup> , 75 <sup>th</sup> , 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)
<b>Hazard Ratio (HR)</b> (95% CI) <i>P</i> value	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
<b>Response Rate (%)</b> (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)

464 TTP = Time to progression.

465 <sup>a</sup> The time from last tumor assessment to the data cut-off date was >100 days in approximately  
466 30% of patients in the independent assessment. The pre-specified assessment interval was 42  
467 or 84 days.

468

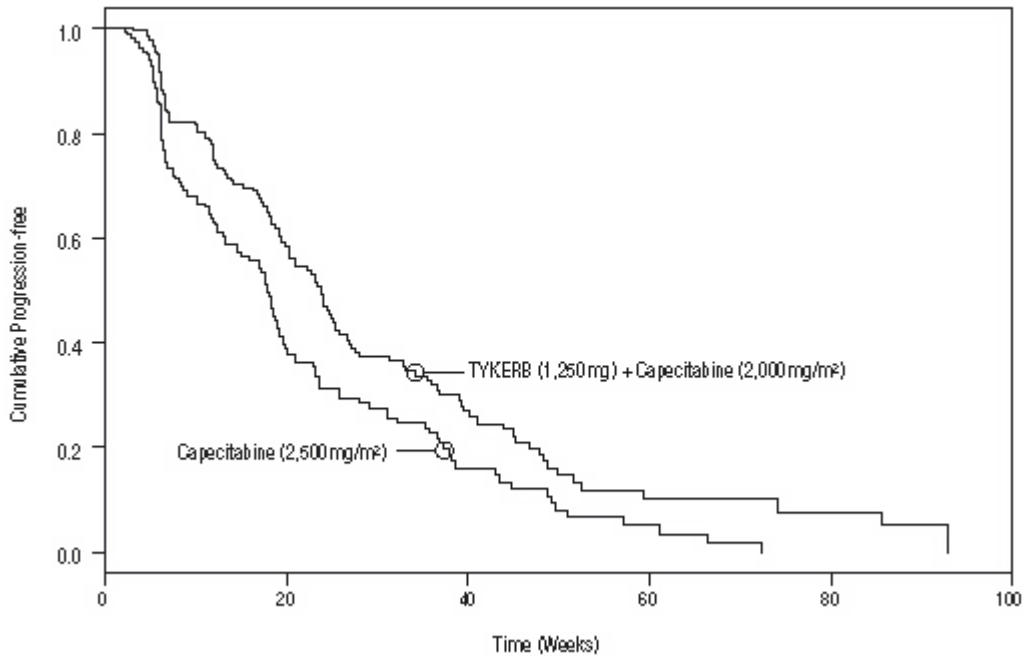
469 **Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to**  
470 **Progression**



471

472

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



474

475

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

481

482 **Table 6: Overall Survival Data**

	<b>TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m<sup>2</sup>/day (N = 207)</b>	<b>Capecitabine 2,500 mg/m<sup>2</sup>/day (N = 201)</b>
<b>Overall Survival</b>		
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	

483 CI = confidence interval.

484

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

486 based chemotherapy regimens have been shown to be less effective than trastuzumab-based  
487 chemotherapy regimens. The first randomized, open-label study compared the safety and  
488 efficacy of TYKERB in combination with capecitabine relative to trastuzumab in combination  
489 with capecitabine in women with HER2-positive metastatic breast cancer (N = 540). The study  
490 was stopped early based on the findings of a pre-planned interim analysis showing a low  
491 incidence of CNS events (primary endpoint) and superior efficacy of the trastuzumab plus  
492 capecitabine. The median progression-free survival was 6.6 months in the group receiving  
493 TYKERB in combination with capecitabine compared with 8.0 months in the group receiving the  
494 trastuzumab combination [HR = 1.30 (95% CI: 1.04, 1.64)]. Overall survival was analyzed when  
495 26% of deaths occurred in the group receiving TYKERB in combination with capecitabine and  
496 22% in the group receiving the trastuzumab combination [HR = 1.34 (95% CI: 0.95, 1.92)].

497 The second randomized, open-label study compared the safety and efficacy of taxane-  
498 based chemotherapy plus TYKERB to taxane-based chemotherapy plus trastuzumab as first-line  
499 therapy in women with HER2-positive, metastatic breast cancer (N = 652). The study was  
500 stopped early based on findings from a pre-planned interim analysis. The median progression-  
501 free survival was 11.3 months in the trastuzumab combination treatment arm compared to  
502 9.0 months in patients treated with TYKERB in the combination arm for the intent-to-treat  
503 population [HR = 1.37 (95% CI: 1.13, 1.65)].

#### 504 **14.2 Hormone Receptor-Positive, HER2-Positive Metastatic Breast Cancer**

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

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

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

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

529  
 530

**Table 7. Efficacy Results**

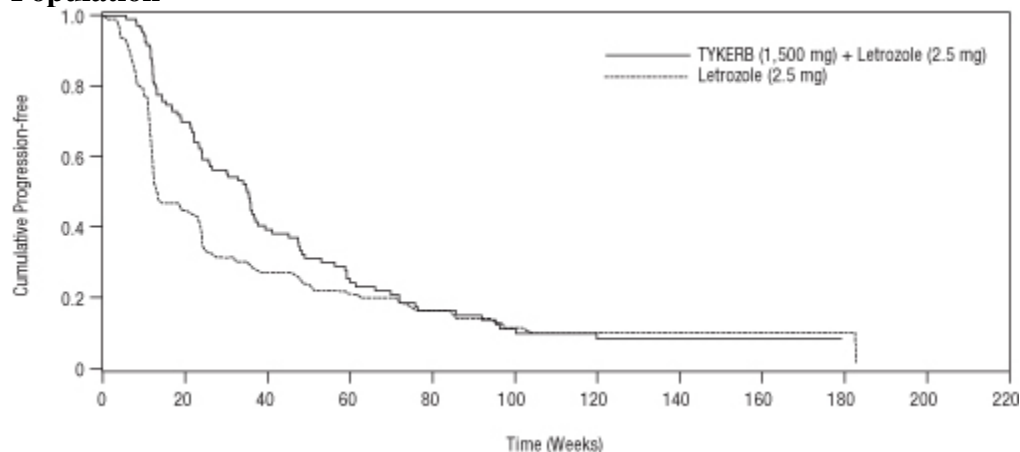
	HER2-Positive Population		HER2-Negative Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
<b>Median PFS<sup>a</sup>, weeks (95% CI)</b>	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)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

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

532 <sup>a</sup> Kaplan-Meier estimate.

533  
 534  
 535

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



536  
 537

538 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

541 Bottles of 150 tablets: NDC 0173-0752-00

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

544 **17 PATIENT COUNSELING INFORMATION**  
545 *See FDA-approved patient labeling (Patient Information).*

546 **17.1 Information for Patients**

547 Patients should be informed of the following:

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

563

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

565



566

567 GlaxoSmithKline

568 Research Triangle Park, NC 27709

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572 TKB:14PI

576 **PATIENT INFORMATION**  
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578 **TYKERB® (TIE-curb)**  
579 **(lapatinib)**  
580 **tablets**  
581

582 Read this leaflet before you start taking TYKERB and each time you get a refill.  
583 There may be new information. This information does not take the place of talking  
584 with your doctor about your medical condition or treatment.  
585

586 **What is TYKERB?**

587 TYKERB is used with the medicine capecitabine for the treatment of people with  
588 advanced or metastatic breast cancer that is HER2-positive (tumors that produce  
589 large amounts of a protein called human epidermal growth factor receptor-2), and  
590 who have already had certain other breast cancer treatments.  
591

592 TYKERB is also used with a type of medicine called letrozole for the treatment of  
593 postmenopausal women with hormone receptor-positive, HER2-positive metastatic  
594 breast cancer for whom hormonal therapy is indicated.  
595

596 It is not known if TYKERB is safe and effective in children.  
597

598 **Who should not take TYKERB?**

599 Do not take TYKERB if you are allergic to any of the ingredients in TYKERB. See the  
600 end of this leaflet for a complete list of ingredients in TYKERB.  
601

602 **What should I tell my doctor before taking TYKERB?**

603 **Before you take TYKERB**, tell your doctor if you:

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

613  
614 **Tell your doctor about all the medicines you take**, including prescription and  
615 over-the-counter medicines, vitamins, and herbal supplements. TYKERB may affect  
616 the way other medicines work, and other medicines may affect the way TYKERB  
617 works.

618  
619 Especially tell your doctor if you take:

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

627  
628 Know the medicines you take. Keep a list of your medicines with you to show your  
629 doctor and pharmacist when you get a new medicine. Do not take other medicines  
630 during treatment with TYKERB without first talking with your doctor.

631  
632 **How should I take TYKERB?**

- 633 • Take TYKERB exactly as your doctor tells you to take it. Your doctor may  
634 change your dose of TYKERB if needed.
- 635 • For people with advanced or metastatic breast cancer, TYKERB and  
636 capecitabine are taken in 21-day cycles. The usual dose of TYKERB is  
637 1,250 mg (5 tablets) taken by mouth all at once, **one time a day on days 1**  
638 **to 21**.
- 639 • Your doctor will tell you the dose of capecitabine you should take and when  
640 you should take it.
- 641 • Take capecitabine with food or within 30 minutes after food.
- 642 • For people with hormone receptor-positive, HER2-positive breast cancer,  
643 TYKERB and letrozole are taken **every day**. The usual dose of TYKERB is  
644 1,500 mg (6 tablets) taken by mouth all at once, **one time a day**. Your  
645 doctor will tell you the dose of letrozole you should take and when you  
646 should take it.
- 647 • TYKERB should be taken at least 1 hour before, or at least 1 hour after a meal.
- 648 • Do not eat or drink grapefruit products during treatment with TYKERB.
- 649 • If you miss a dose of TYKERB, take your next dose at your regular time the  
650 next day.
- 651 • If you take too much TYKERB, call your doctor or go to the nearest hospital  
652 emergency room right away.



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**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.
- **severe skin reactions**. TYKERB may cause severe skin reactions. Tell your doctor right away if you develop a skin rash, blisters, or peeling of the skin. As severe skin reactions can be life-threatening, your doctor may tell you to stop taking TYKERB.

**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

- 693 • rash
- 694 • vomiting
- 695 • tiredness or weakness
- 696 • mouth sores
- 697 • loss of appetite
- 698 • indigestion
- 699 • unusual hair loss or thinning
- 700 • nose bleeds
- 701 • headache
- 702 • dry skin
- 703 • itching
- 704 • nail disorders such as nail bed changes, nail pain, infection and swelling of the
- 705 cuticles.

706

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

709

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

712

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

715

716 **You may also get side effects from the other medicines taken with TYKERB.**

717 Talk to your doctor about possible side effects you may get during treatment.

718

719 **How should I store TYKERB Tablets?**

- 720 • Store TYKERB Tablets at room temperature between 68° and 77°F (20° and
- 721 25°C).
- 722 • Keep the container closed tightly.
- 723 • Do not keep medicine that is out of date or that you no longer need.

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

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727 **General information about TYKERB**

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

732

733 This leaflet summarizes the most important information about TYKERB. If you  
734 would like more information, talk with your doctor. You can ask your doctor or  
735 pharmacist for information about TYKERB that is written for health professionals.  
736

737 For more information, call 1-888-825-5249 or go to [www.tykerb.com](http://www.tykerb.com).  
738

739 **What are the ingredients in TYKERB?**

740 **Active ingredient:** Lapatinib.

741 **Inactive ingredients: Tablet Core:** Magnesium stearate, microcrystalline  
742 cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat: FD&C  
743 yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400,  
744 polysorbate 80, titanium dioxide.  
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747 This Patient Information has been approved by the U.S. Food and Drug  
748 Administration.

749 TYKERB is a registered trademark of the GlaxoSmithKline group of companies.  
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/s/  
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AMY E MCKEE

12/22/2014

Acting for Dr. Amna Ibrahim.