

## 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

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

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.
- 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 1500 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)

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#### 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 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](http://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 (ABC1). (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)

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Revised: 06/2013

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

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

## 16 **2 DOSAGE AND ADMINISTRATION**

### 17 **2.1 Recommended Dosing**

18 HER2 Positive Metastatic Breast Cancer: The recommended dose of TYKERB is  
19 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine  
20 2,000 mg/m<sup>2</sup>/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in  
21 a repeating 21 day cycle. TYKERB should be taken at least one hour before or one hour after a  
22 meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing  
23 the daily dose is not recommended [see *Clinical Pharmacology (12.3)*]. Capecitabine should be  
24 taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not  
25 double the dose the next day. Treatment should be continued until disease progression or  
26 unacceptable toxicity occurs.

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

### 33 **2.2 Dose Modification Guidelines**

34 Cardiac Events: TYKERB should be discontinued in patients with a decreased left  
35 ventricular ejection fraction (LVEF) that is Grade 2 or greater by National Cancer Institute  
36 Common Terminology Criteria for Adverse Events (NCI CTCAE v3) and in patients with an

37 LVEF that drops below the institution's lower limit of normal [*see Warnings and Precautions*  
38 (5.1) and *Adverse Reactions* (6.1)]. TYKERB in combination with capecitabine may be restarted  
39 at a reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at a  
40 reduced dose of 1,250 mg/day after a minimum of 2 weeks if the LVEF recovers to normal and  
41 the patient is asymptomatic.

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

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

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

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

77 *Interactions (7.2).]*

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

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

### 86 **3 DOSAGE FORMS AND STRENGTHS**

87 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one  
88 side.

### 89 **4 CONTRAINDICATIONS**

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

### 92 **5 WARNINGS AND PRECAUTIONS**

#### 93 **5.1 Decreased Left Ventricular Ejection Fraction**

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

#### 102 **5.2 Hepatotoxicity**

103 Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin  
104 >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and  
105 postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.  
106 Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after  
107 initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase)  
108 should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as  
109 clinically indicated. If changes in liver function are severe, therapy with TYKERB should be  
110 discontinued and patients should not be retreated with TYKERB [*see Adverse Reactions (6.1)*].

#### 111 **5.3 Patients with Severe Hepatic Impairment**

112 If TYKERB is to be administered to patients with severe pre-existing hepatic impairment,  
113 dose reduction should be considered [*see Dosage and Administration (2.2) and Use in Specific*  
114 *Populations (8.7)*]. In patients who develop severe hepatotoxicity while on therapy, TYKERB

115 should be discontinued and patients should not be retreated with TYKERB [see Warnings and  
116 Precautions (5.2)].

#### 117 **5.4 Diarrhea**

118 Diarrhea has been reported during treatment with TYKERB [see Adverse Reactions  
119 (6.1)]. The diarrhea may be severe, and deaths have been reported. Diarrhea generally occurs  
120 early during treatment with TYKERB, with almost half of those patients with diarrhea first  
121 experiencing it within 6 days. This usually lasts 4 to 5 days. Lapatinib-induced diarrhea is  
122 usually low-grade, with severe diarrhea of NCI CTCAE Grades 3 and 4 occurring in <10% and  
123 <1% of patients, respectively. Early identification and intervention is critical for the optimal  
124 management of diarrhea. Patients should be instructed to report any change in bowel patterns  
125 immediately. Prompt treatment of diarrhea with anti-diarrheal agents (such as loperamide) after  
126 the first unformed stool is recommended. Severe cases of diarrhea may require administration of  
127 oral or intravenous electrolytes and fluids, use of antibiotics such as fluoroquinolones (especially  
128 if diarrhea is persistent beyond 24 hours, there is fever, or Grade 3 or 4 neutropenia), and  
129 interruption or discontinuation of therapy with TYKERB [(see Dosage and Administration  
130 (2.2)].

#### 131 **5.5 Interstitial Lung Disease/Pneumonitis**

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

#### 137 **5.6 QT Prolongation**

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

#### 145 **5.7 Use in Pregnancy**

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

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

154 **6 ADVERSE REACTIONS**

155 **6.1 Clinical Trials Experience**

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

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

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

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

170

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

Reactions	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)		
	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

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

173 <sup>b</sup> Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine  
174 group.

175

176 **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

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

178

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

187

188 **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

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

190 <sup>b</sup> In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional  
191 subjects in each treatment arm had rash under "Infections and infestations"; none were Grade  
192 3 or 4.

193

194 **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

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

196

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

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

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

## 212 **6.2 Postmarketing Experience**

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

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

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

## 220 **7 DRUG INTERACTIONS**

### 221 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport 222 Systems**

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

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

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

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

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

## 241 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

247 Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at  
248 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to  
249 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

250 Carbamazepine: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at  
251 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to  
252 lapatinib was decreased approximately 72%.

## 253 **7.3 Drugs that Inhibit Drug Transport Systems**

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

## 257 **7.4 Acid Reducing Agents**

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

# 262 **8 USE IN SPECIFIC POPULATIONS**

## 263 **8.1 Pregnancy**

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

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

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

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

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

### 289 **8.3 Nursing Mothers**

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

### 294 **8.4 Pediatric Use**

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

### 296 **8.5 Geriatric Use**

297 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in  
298 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were  
299 75 years of age and older. Of the total number of hormone receptor positive, HER2 positive  
300 metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole  
301 (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No  
302 overall differences in safety or effectiveness were observed between elderly subjects and  
303 younger subjects, and other reported clinical experience has not identified differences in  
304 responses between the elderly and younger patients, but greater sensitivity of some older  
305 individuals cannot be ruled out.

306 **8.6 Renal Impairment**

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

312 **8.7 Hepatic Impairment**

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

323 **10 OVERDOSAGE**

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

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

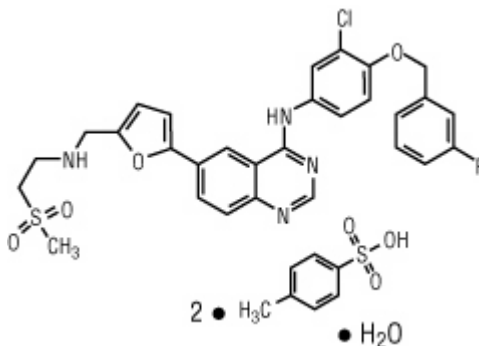
334 Because lapatinib is not significantly renally excreted and is highly bound to plasma  
335 proteins, hemodialysis would not be expected to be an effective method to enhance the  
336 elimination of lapatinib.

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

338 **11 DESCRIPTION**

339 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase  
340 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-  
341 chloro-4-[(3-fluorophenyl)methyl]oxy)phenyl)-6-[5-({[2-  
342 (methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-  
343 methylbenzenesulfonate) monohydrate. It has the molecular formula C<sub>29</sub>H<sub>26</sub>ClFN<sub>4</sub>O<sub>4</sub>S  
344 (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

345 following chemical structure:



346

347 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is  
348 0.001 mg/mL at 25°C.

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

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

## 355 12 CLINICAL PHARMACOLOGY

### 356 12.1 Mechanism of Action

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

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

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

### 372 12.3 Pharmacokinetics

373 Absorption: Absorption following oral administration of TYKERB is incomplete and  
374 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to  
375 1.5 hour). Peak plasma concentrations ( $C_{max}$ ) of lapatinib are achieved approximately 4 hours

376 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to  
377 7 days, indicating an effective half-life of 24 hours.

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

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

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

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

392 **Metabolism:** Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and  
393 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated  
394 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or  
395 10% of lapatinib concentration in plasma.

396 **Elimination:** At clinical doses, the terminal phase half-life following a single dose was  
397 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

398 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with  
399 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of  
400 27% (range 3 to 67%) of an oral dose.

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

#### 403 **12.4 QT Prolongation**

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

### 409 **13 NONCLINICAL TOXICOLOGY**

#### 410 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

411 Two-year carcinogenicity studies with lapatinib are ongoing.

412 Lapatinib was not clastogenic or mutagenic in the Chinese hamster ovary chromosome  
413 aberration assay, microbial mutagenesis (Ames) assay, human lymphocyte chromosome  
414 aberration assay or the in vivo rat bone marrow chromosome aberration assay at single doses up

415 to 2,000 mg/kg. However, an impurity in the drug product (up to 4 ppm or 8 mcg/day) was  
416 genotoxic when tested alone in both in vitro and in vivo assays.

417 There were no effects on male or female rat mating or fertility at doses up to  
418 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times  
419 the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus  
420 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,  
421 when female rats were given oral doses of lapatinib during breeding and through the first 6 days  
422 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and  
423 in the fetal body weights at  $\geq 60$  mg/kg/day (approximately 6.4 times and 3.3 times the expected  
424 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine,  
425 respectively).

## 426 **14 CLINICAL STUDIES**

### 427 **14.1 HER2 Positive Metastatic Breast Cancer**

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

433 Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously)  
434 plus capecitabine 2,000 mg/m<sup>2</sup>/day on Days 1-14 every 21 days, or to receive capecitabine alone  
435 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  
436 (TTP). TTP was defined as time from randomization to tumor progression or death related to  
437 breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was  
438 discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The  
439 median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were  
440 Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+  
441 (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH  
442 confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes,  
443 and trastuzumab.

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

446

447 **Table 5. Efficacy Results**

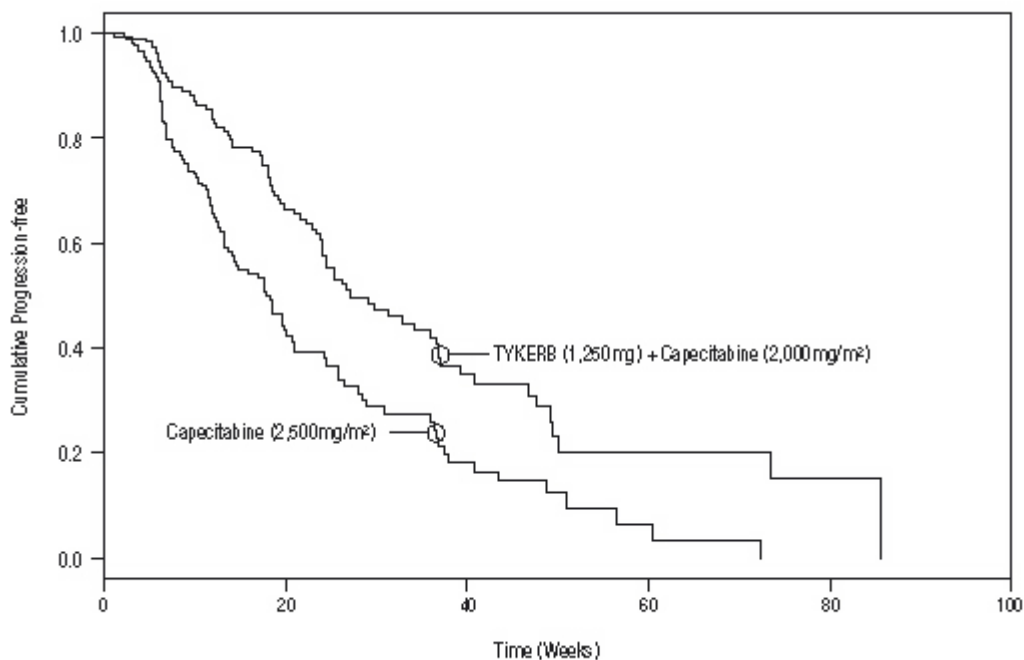
	Independent Assessment <sup>a</sup>		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m <sup>2</sup> /day	Capecitabine 2,500 mg/m <sup>2</sup> /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m <sup>2</sup> /day	Capecitabine 2,500 mg/m <sup>2</sup> /day
	(N = 198)	(N = 201)	(N = 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</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)

448 TTP = Time to progression.

449 <sup>a</sup> The time from last tumor assessment to the data cut-off date was >100 days in approximately  
 450 30% of patients in the independent assessment. The pre-specified assessment interval was 42  
 451 or 84 days.

452

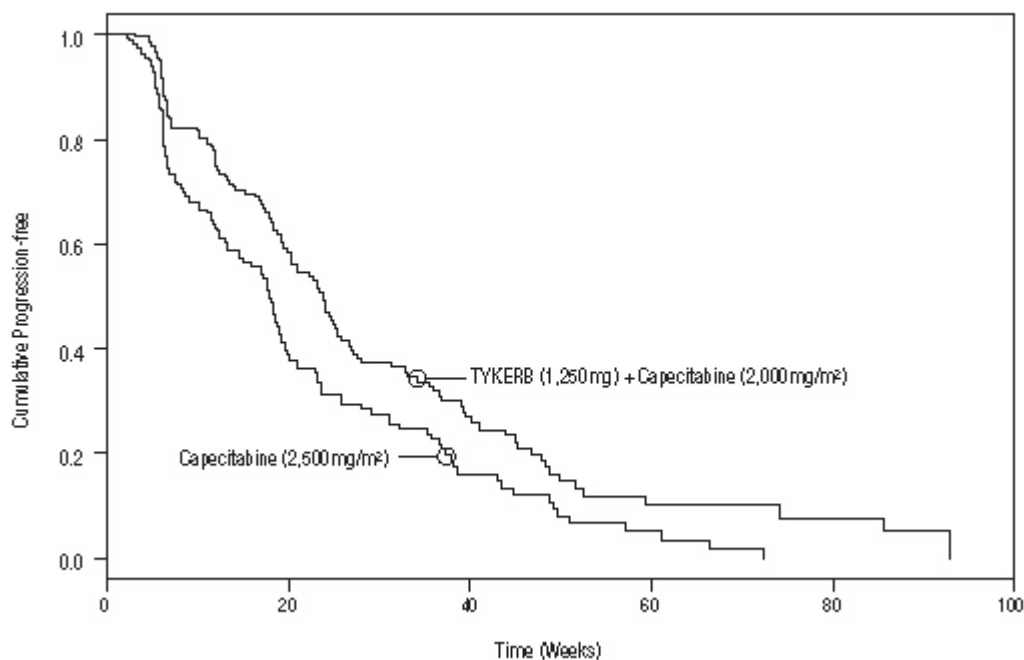
453 **Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to**  
 454 **Progression**



455

456

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



458

459

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

465

466

**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	

467

CI = confidence interval

468

469 **14.2 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer**

470

The efficacy and safety of TYKERB in combination with letrozole were evaluated in a

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

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

487 In the HER2 positive subgroup (n = 219), the addition of TYKERB to letrozole resulted  
488 in an improvement in PFS. In the HER2 negative subgroup, there was no improvement in PFS of  
489 the TYKERB plus letrozole combination compared to the letrozole plus placebo. Overall  
490 response rate (ORR) was also improved with the TYKERB plus letrozole combination therapy.  
491 The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor  
492 positive, HER2 positive and HER2 negative subgroups are presented in Table 7 and Figure 3.  
493

494 **Table 7. Efficacy Results**

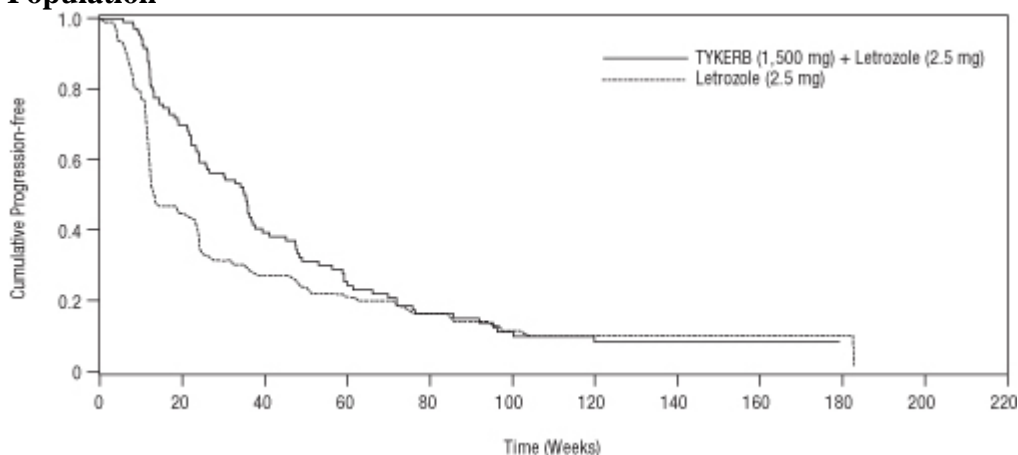
	HER2(+) Population		HER2(-) Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
<b>Median PFS<sup>a</sup>, weeks (95% CI)</b>	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 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)

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

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

497

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



500  
501

## 502 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

## 508 **17 PATIENT COUNSELING INFORMATION**

509 See FDA-approved patient labeling (17.2).

### 510 **17.1 Information for Patients**

511 Patients should be informed of the following:

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

527 **17.2 FDA-Approved Patient Labeling**

528 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing  
529 information.

530

531 TYKERB is a registered trademark of GlaxoSmithKline.

532



533

534 GlaxoSmithKline

535 Research Triangle Park, NC 27709

536

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538

539 TKB:XPI

540 PHARMACIST - DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

541 -----

542

543

## PATIENT INFORMATION

544

545

### TYKERB (TIE-curb)

546

### (lapatinib) tablets

547

548 Read this leaflet before you start taking TYKERB<sup>®</sup> and each time you get a refill.

549 There may be new information. This information does not take the place of talking  
550 with your doctor about your medical condition or treatment.

551

#### 552 **What is TYKERB?**

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

557

558 TYKERB is also used with a type of medicine called letrozole for the treatment of  
559 postmenopausal women with hormone receptor positive, HER2 positive metastatic  
560 breast cancer for whom hormonal therapy is indicated. TYKERB in combination with  
561 an aromatase inhibitor has not been compared to a trastuzumab-containing  
562 chemotherapy regimen for the treatment of metastatic breast cancer.

563

#### 564 **Who should not take TYKERB?**

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

567

568 **Before you start taking TYKERB**, tell your doctor about all of your medical  
569 conditions, including if you:

- 570 • ever had a severe allergic (hypersensitivity) reaction to TYKERB. Check with  
571 your doctor if you think this applies to you. Don't take TYKERB.
- 572 • have heart problems.
- 573 • have liver problems. You may need a lower dose of TYKERB.
- 574 • are pregnant or may become pregnant. TYKERB may harm an unborn baby. If  
575 you become pregnant during treatment with TYKERB, tell your doctor as soon  
576 as possible.
- 577 • are breast-feeding. It is not known if TYKERB passes into your breast milk or if  
578 it can harm your baby. If you are a woman who has or will have a baby, talk  
579 with your doctor about the best way to feed your baby.

580

581 Tell your doctor about all the medicines you take, including prescription and  
582 nonprescription medicines, vitamins, and herbal and dietary supplements. TYKERB  
583 and many other medicines may interact with each other. Your doctor needs to know  
584 what medicines you take so he or she can choose the right dose of TYKERB for you.  
585

586 Especially tell your doctor if you take:

- 587 • antibiotics and anti-fungals (drugs used to treat infections)
- 588 • HIV (AIDS) treatments
- 589 • anticonvulsant drugs (drugs used to treat seizures)
- 590 • calcium channel blockers (drugs used to treat certain heart disorders or high  
591 blood pressure)
- 592 • antidepressants
- 593 • drugs that decrease stomach acidity
- 594 • St. John's Wort or other herbal supplements

595

596 Know the medicines you take. Keep a list of your medicines with you to show your  
597 doctor. Do not take other medicines during treatment with TYKERB without first  
598 checking with your doctor.  
599

600 Because TYKERB is given with other drugs called capecitabine or letrozole, you  
601 should also discuss with your doctor or pharmacist any medicines that should be  
602 avoided during treatment.  
603

#### 604 **How should I take TYKERB?**

- 605 • Take TYKERB exactly as your doctor tells you to take it. Your doctor may  
606 change your dose of TYKERB if needed.
- 607 • For patients with advanced or metastatic breast cancer, TYKERB and  
608 capecitabine are taken in 21 day cycles. The usual dose of TYKERB is 1,250  
609 mg (5 tablets) taken by mouth all at once, **one time a day on days 1 to**  
610 **21**. Your doctor will tell you the dose of capecitabine you should take and  
611 when you should take it.
- 612 • For patients with hormone receptor positive, HER2 positive breast cancer,  
613 TYKERB and letrozole are taken daily. The usual dose of TYKERB is 1,500 mg  
614 (6 tablets) taken by mouth all at once, **one time a day**. Your doctor will tell  
615 you the dose of letrozole you should take and when you should take it.
- 616 • TYKERB should be taken at least one hour before, or at least one hour after  
617 food.
- 618 • Do not eat or drink grapefruit products while taking TYKERB.
- 619 • If you forget to take your dose of TYKERB, do not take two doses at one time.  
620 Take your next dose at your scheduled time.

- 621 • If you take too much TYKERB, call your doctor or poison control center, or go to  
622 the nearest hospital emergency room right away. Take TYKERB tablets with you  
623 when possible.  
624

625 **What are the possible side effects of TYKERB?**

626 **Serious side effects** include:

- 627 • **heart problems** including, decreased pumping of blood from the heart and an  
628 abnormal heartbeat. Signs and symptoms of an abnormal heartbeat include:  
629 • feeling like your heart is pounding or racing  
630 • dizziness  
631 • tiredness  
632 • feeling lightheaded  
633 • shortness of breath  
634 • Your doctor should check your heart function before you start taking  
635 TYKERB and during treatment.
- 636 • **liver problems.** Signs and symptoms of liver problems include:  
637 • itching  
638 • yellow eyes or skin  
639 • dark urine  
640 • pain or discomfort in the right upper stomach area  
641 • death  
642 • Your doctor should do blood tests to check your liver before you start  
643 taking TYKERB and during treatment.
- 644 • **diarrhea**, which may cause you to become dehydrated. Follow your doctors  
645 instructions for what to do to help prevent or treat diarrhea. Call your doctor  
646 immediately at the first sign of diarrhea, as it is important that this is treated  
647 right away.
- 648 • **lung problems.** Symptoms of a lung problem with TYKERB include a cough  
649 that will not go away or shortness of breath.  
650

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

653  
654 **Common side effects** of TYKERB in combination with capecitabine or letrozole  
655 include:

- 656 • diarrhea  
657 • red, painful hands and feet  
658 • nausea  
659 • rash  
660 • vomiting

- 661 • tiredness or weakness
- 662 • mouth sores
- 663 • loss of appetite
- 664 • indigestion
- 665 • unusual hair loss or thinning
- 666 • nose bleeds
- 667 • headache
- 668 • dry skin
- 669 • itching
- 670 • nail disorders such as nail bed changes, nail pain, infection and swelling of the
- 671 cuticles.

672

673 Tell your doctor about any side effect that gets serious or that does not go away.

674

675 These are not all the side effects with TYKERB. Ask your doctor or pharmacist for  
676 more information.

677

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

680

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

683

#### 684 **How should I store TYKERB tablets?**

- 685 • Store TYKERB tablets at room temperature at 59° to 86°F (15° to 30°C). Keep  
686 the container closed tightly.
- 687 • Do not keep medicine that is out of date or that you no longer need. Be sure  
688 that if you throw any medicine away, it is out of the reach of children.
- 689 • **Keep TYKERB and all medicines out of the reach of children.**

690

#### 691 **General information about TYKERB**

692 Medicines are sometimes prescribed for conditions that are not mentioned in  
693 patient information leaflets. Do not use TYKERB for any other condition for which it  
694 was not prescribed. Do not give TYKERB to other people, even if they have the  
695 same condition that you have. It may harm them.

696

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

700 For more information, you can call toll-free 1-888-825-5249 or by visiting the

701 website [www.tykerb.com](http://www.tykerb.com).

702

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

704 **Active Ingredient:** Lapatinib.

705 **Inactive Ingredients: Tablet Core:** Magnesium stearate, microcrystalline  
706 cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat: FD&C  
707 yellow #6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400,  
708 polysorbate 80, titanium dioxide.

709

710 TYKERB tablets are oval, biconvex, orange, film-coated with GS XJG printed on one  
711 side.



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