

## 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

Indications and Usage. (1)	Month Year
Dosage and Administration. (2)	Month Year
Contraindications. (4)	Month Year

### 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 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, and CYP3A4 drug interactions. (2.2)

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### FULL PRESCRIBING INFORMATION

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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, 12.6)
- 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 metabolized by CYP3A4 or CYP2C8. (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: Month Year

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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) and in patients with an LVEF  
37 that drops below the institution's lower limit of normal [*see Warnings and Precautions (5.1) and*  
38 *Adverse Reactions (6.1)*]. TYKERB in combination with capecitabine may be restarted at a  
39 reduced dose (1,000 mg/day) and in combination with letrozole may be restarted at a reduced  
40 dose of 1,250 mg/day after a minimum of 2 weeks if the LVEF recovers to normal and the  
41 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 **Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4  
50 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir,  
51 indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit  
52 may also increase plasma concentrations of lapatinib and should be avoided. If patients must be  
53 coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction  
54 to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without  
55 inhibitors and should be considered. However, there are no clinical data with this dose  
56 adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is  
57 discontinued, a washout period of approximately 1 week should be allowed before the lapatinib  
58 dose is adjusted upward to the indicated dose. [*See Drug Interactions (7.2).*]

59 **Concomitant Strong CYP3A4 Inducers:** The concomitant use of strong CYP3A4  
60 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin,  
61 rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered a strong CYP3A4  
62 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually  
63 from 1,250 mg/day up to 4,500 mg/day (HER2 positive metastatic breast cancer indication) or  
64 from 1,500 mg/day up to 5,500 mg/day (hormone receptor positive, HER2 positive breast cancer  
65 indication) based on tolerability. This dose of lapatinib is predicted to adjust the lapatinib AUC  
66 to the range observed without inducers and should be considered. However, there are no clinical  
67 data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong  
68 inducer is discontinued the lapatinib dose should be reduced to the indicated dose. [*See Drug*  
69 *Interactions (7.2).*]

70 **Other Toxicities:** Discontinuation or interruption of dosing with TYKERB may be  
71 considered when patients develop  $\geq$ Grade 2 NCI CTCAE toxicity and can be restarted at  
72 1,250 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then  
73 TYKERB in combination with capecitabine should be restarted at a lower dose (1,000 mg/day)  
74 and in combination with letrozole should be restarted at a lower dose of 1,250 mg/day.

75 **See manufacturer's prescribing information for the coadministered product dosage**

76 **adjustment guidelines in the event of toxicity and other relevant safety information or**  
77 **contraindications.**

### 78 **3 DOSAGE FORMS AND STRENGTHS**

79 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one  
80 side.

### 81 **4 CONTRAINDICATIONS**

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

### 84 **5 WARNINGS AND PRECAUTIONS**

#### 85 **5.1 Decreased Left Ventricular Ejection Fraction**

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

#### 94 **5.2 Hepatotoxicity**

95 Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin  
96 >2 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and  
97 postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.  
98 Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after  
99 initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase)  
100 should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as  
101 clinically indicated. If changes in liver function are severe, therapy with TYKERB should be  
102 discontinued and patients should not be retreated with TYKERB [*see Adverse Reactions (6.1)*].

#### 103 **5.3 Patients with Severe Hepatic Impairment**

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

#### 109 **5.4 Diarrhea**

110 Diarrhea, including severe diarrhea, has been reported during treatment with TYKERB  
111 [*see Adverse Reactions (6.1)*]. Proactive management of diarrhea with anti-diarrheal agents is  
112 important. Severe cases of diarrhea may require administration of oral or intravenous electrolytes  
113 and fluids, and interruption or discontinuation of therapy with TYKERB.

114 **5.5 Interstitial Lung Disease/Pneumonitis**

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

120 **5.6 QT Prolongation**

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

128 **5.7 Use in Pregnancy**

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

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

137 **6 ADVERSE REACTIONS**

138 **6.1 Clinical Trials Experience**

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

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

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

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

153

154

**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

155

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

156

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

157

158

159 **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

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

161  
 162 Hormone Receptor Positive, Metastatic Breast Cancer: In a randomized clinical  
 163 trial of patients (N = 1,286) with hormone receptor positive, metastatic breast cancer, who had  
 164 not received chemotherapy for their metastatic disease, patients received letrozole with or  
 165 without TYKERB. In this trial, the safety profile of TYKERB was consistent with previously  
 166 reported results from trials of TYKERB in the advanced or metastatic breast cancer population.  
 167 Adverse reactions which occurred in at least 10% of patients in either treatment arm and were  
 168 higher in the combination arm are shown in Table 3. Selected laboratory abnormalities are  
 169 shown in Table 4.  
 170

171 **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

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

173 <sup>b</sup> In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional  
 174 subjects in each treatment arm had rash under "Infections and infestations"; none were Grade  
 175 3 or 4.

176



177 **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

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

179  
 180 **Decreases in Left Ventricular Ejection Fraction:** Due to potential cardiac toxicity  
 181 with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week  
 182 intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular  
 183 cardiac function that are ≥Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac  
 184 ejection fraction relative to baseline which is below the institution's lower limit of normal.  
 185 Among 198 patients who received TYKERB/capecitabine combination treatment, 3 experienced  
 186 Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTCAE v3). [See Warnings and  
 187 Precautions (5.1).] Among 654 patients who received TYKERB/letrozole combination  
 188 treatment, 26 patients experienced Grade 1 or 2 and 6 patients had Grade 3 or 4 LVEF adverse  
 189 reactions.

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

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

## 195 **6.2 Postmarketing Experience**

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

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

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

## 203 **7 DRUG INTERACTIONS**

### 204 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport** 205 **Systems**

206 Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations.  
 207 Caution should be exercised and dose reduction of the concomitant substrate drug should be  
 208 considered when dosing lapatinib concurrently with medications with narrow therapeutic  
 209 windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the

210 following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or  
211 UGT enzymes in vitro, however, the clinical significance is unknown.

212 Lapatinib inhibits human P-glycoprotein. If TYKERB is administered with drugs that are  
213 substrates of P-gp, increased concentrations of the substrate drug are likely, and caution should  
214 be exercised.

215 **Paclitaxel:** In cancer patients receiving TYKERB and the CYP2C8 substrate paclitaxel,  
216 24-hour systemic exposure (AUC) of paclitaxel was increased 23%. This increase in paclitaxel  
217 exposure may have been underestimated from the in vivo evaluation due to study design  
218 limitations.

## 219 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

225 **Ketoconazole:** In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at  
226 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to  
227 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

228 **Carbamazepine:** In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at  
229 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to  
230 lapatinib was decreased approximately 72%.

## 231 **7.3 Drugs that Inhibit Drug Transport Systems**

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

# 235 **8 USE IN SPECIFIC POPULATIONS**

## 236 **8.1 Pregnancy**

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

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

246 In a study where pregnant rats were dosed with lapatinib during organogenesis and  
247 through lactation, at a dose of 120 mg/kg/day (approximately 6.4 times the human clinical  
248 exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine), 91% of the

249 pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were dead. The  
250 highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the human  
251 clinical exposure based on AUC).

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

### 262 **8.3 Nursing Mothers**

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

### 267 **8.4 Pediatric Use**

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

### 269 **8.5 Geriatric Use**

270 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in  
271 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were  
272 75 years of age and older. Of the total number of hormone receptor positive, HER2 positive  
273 metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole  
274 (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No  
275 overall differences in safety or effectiveness were observed between elderly subjects and  
276 younger subjects, and other reported clinical experience has not identified differences in  
277 responses between the elderly and younger patients, but greater sensitivity of some older  
278 individuals cannot be ruled out.

### 279 **8.6 Renal Impairment**

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

### 285 **8.7 Hepatic Impairment**

286 The pharmacokinetics of lapatinib were examined in subjects with pre-existing moderate  
287 (n = 8) or severe (n = 4) hepatic impairment (Child-Pugh Class B/C, respectively) and in 8  
288 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose

289 increased approximately 14% and 63% in subjects with moderate and severe pre-existing hepatic  
290 impairment, respectively. Administration of TYKERB in patients with severe hepatic  
291 impairment should be undertaken with caution due to increased exposure to the drug. A dose  
292 reduction should be considered for patients with severe pre-existing hepatic impairment [see  
293 *Dosage and Administration (2.2)*]. In patients who develop severe hepatotoxicity while on  
294 therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB  
295 [see *Warnings and Precautions (5.2)*].

## 296 **10 OVERDOSAGE**

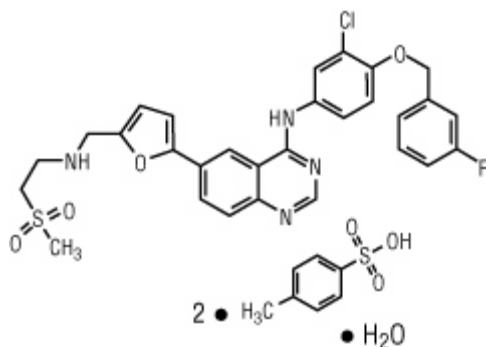
297 There is no known antidote for overdoses of TYKERB. The maximum oral doses of  
298 lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent  
299 ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical  
300 trials and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

302 There has been a report of one patient who took 3,000 mg of TYKERB for 10 days. This  
303 patient had Grade 3 diarrhea and vomiting on Day 10. The event resolved following IV hydration  
304 and interruption of treatment with TYKERB and letrozole.

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

## 308 **11 DESCRIPTION**

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



316

317 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is  
318 0.001 mg/mL at 25°C.

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

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

## 325 **12 CLINICAL PHARMACOLOGY**

### 326 **12.1 Mechanism of Action**

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

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

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

### 342 **12.3 Pharmacokinetics**

343 Absorption: Absorption following oral administration of TYKERB is incomplete and  
344 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to  
345 1.5 hour). Peak plasma concentrations ( $C_{max}$ ) of lapatinib are achieved approximately 4 hours  
346 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to  
347 7 days, indicating an effective half-life of 24 hours.

348 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)  
349 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  
350 to 56 mcg.hr/mL).

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

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

357 Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid

358 glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast  
359 cancer resistance protein (BCRP, ABCG2) and P-glycoprotein (P-gp, ABCB1). Lapatinib has  
360 also been shown in vitro to inhibit these efflux transporters, as well as the hepatic uptake  
361 transporter OATP 1B1, at clinically relevant concentrations.

362 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and  
363 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated  
364 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or  
365 10% of lapatinib concentration in plasma.

366 Elimination: At clinical doses, the terminal phase half-life following a single dose was  
367 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

368 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with  
369 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of  
370 27% (range 3 to 67%) of an oral dose.

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

#### 373 **12.4 QT Prolongation**

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

### 379 **13 NONCLINICAL TOXICOLOGY**

#### 380 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

381 Two-year carcinogenicity studies with lapatinib are ongoing.

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

387 There were no effects on male or female rat mating or fertility at doses up to  
388 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times  
389 the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus  
390 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,  
391 when female rats were given oral doses of lapatinib during breeding and through the first 6 days  
392 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and  
393 in the fetal body weights at  $\geq 60$  mg/kg/day (approximately 6.4 times and 3.3 times the expected  
394 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine,  
395 respectively).

396 **14 CLINICAL STUDIES**

397 **14.1 HER2 Positive Metastatic Breast Cancer**

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

403 Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously)  
 404 plus capecitabine 2,000 mg/m<sup>2</sup>/day on Days 1-14 every 21 days, or to receive capecitabine alone  
 405 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  
 406 (TTP). TTP was defined as time from randomization to tumor progression or death related to  
 407 breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was  
 408 discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The  
 409 median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were  
 410 Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+  
 411 (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH  
 412 confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes,  
 413 and trastuzumab.

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

416

417 **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)

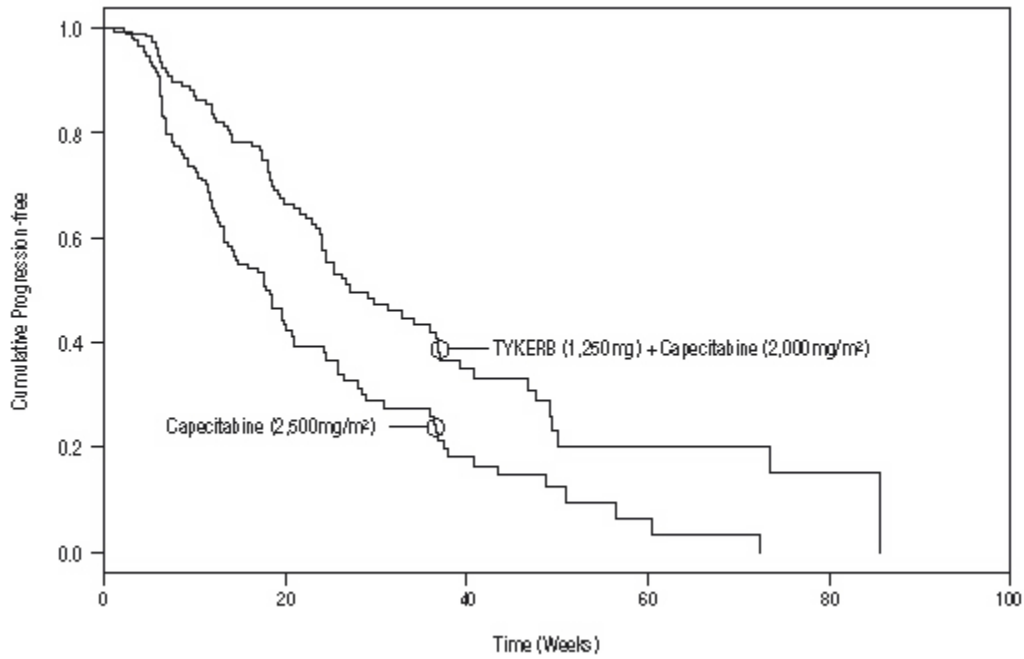
418 TTP = Time to progression.

419 <sup>a</sup> The time from last tumor assessment to the data cut-off date was >100 days in approximately

420 30% of patients in the independent assessment. The pre-specified assessment interval was 42  
421 or 84 days.

422

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

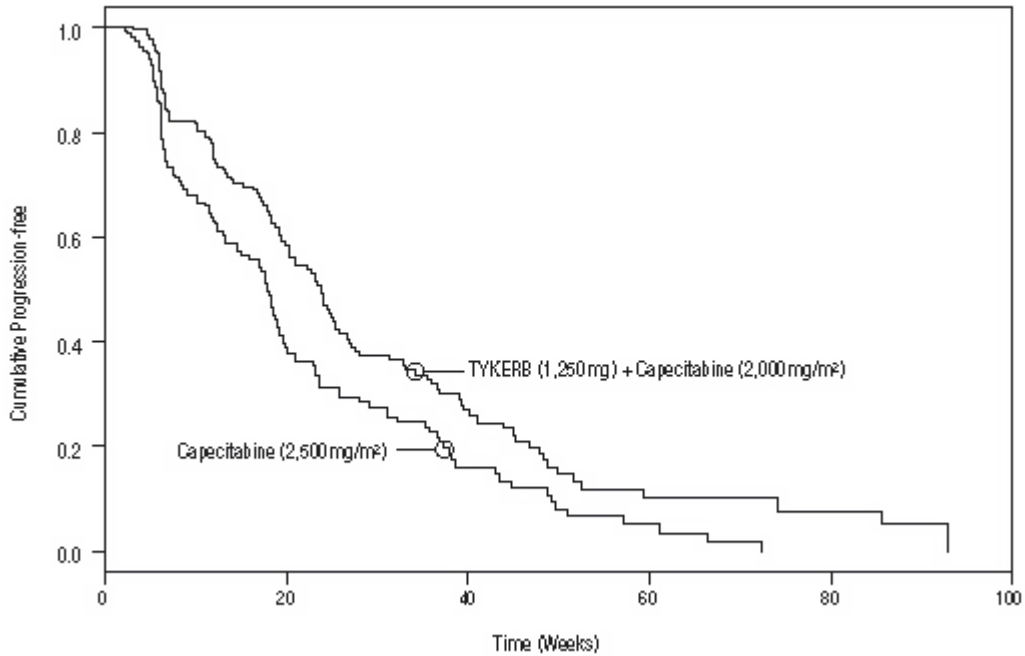


425

426



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



428  
429

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

435  
436

**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 ( <i>P</i> value)	0.89 (0.71, 1.10) 0.276	

437 CI = confidence interval  
438

439 **14.2 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer**

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

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

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

457 In the HER2 positive subgroup (n = 219), the addition of TYKERB to letrozole resulted  
 458 in an improvement in PFS. In the HER2 negative subgroup, there was no improvement in PFS of  
 459 the TYKERB plus letrozole combination compared to the letrozole plus placebo. Overall  
 460 response rate (ORR) was also improved with the TYKERB plus letrozole combination therapy.  
 461 The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor  
 462 positive, HER2 positive and HER2 negative subgroups are presented in Table 7 and Figure 3.  
 463

464 **Table 7. Efficacy Results**

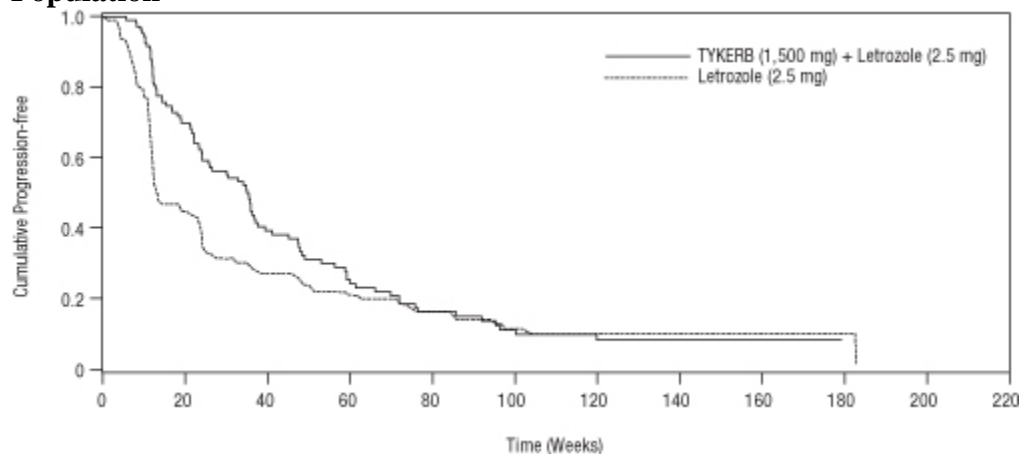
	HER2(+) Population		HER2(-) Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
<b>Median PFS<sup>a</sup>, weeks (95% CI)</b>	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6,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

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

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

467

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



470  
471

## 472 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

## 478 **17 PATIENT COUNSELING INFORMATION**

479 *See FDA-approved patient labeling (17.2).*

### 480 **17.1 Information for Patients**

481 Patients should be informed of the following:

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

497 **17.2 FDA-Approved Patient Labeling**

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

500  
501 TYKERB is a registered trademark of GlaxoSmithKline.  
502



503  
504 GlaxoSmithKline  
505 Research Triangle Park, NC 27709

506  
507 ©Year, GlaxoSmithKline. All rights reserved.

508  
509 Month YEAR  
510 TKB:XPI



513  
514 **PATIENT INFORMATION**

515  
516 **TYKERB (TIE-curb)**  
517 **(lapatinib) tablets**  
518

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

522  
523 **What is TYKERB?**

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

528  
529 TYKERB is also used with a type of medicine called letrozole for the treatment of  
530 postmenopausal women with hormone receptor positive, HER2 positive metastatic breast cancer  
531 for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor  
532 has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of  
533 metastatic breast cancer.

534  
535 **Who should not take TYKERB?**

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

538  
539 **Before you start taking TYKERB**, tell your doctor about all of your medical conditions,  
540 including if you:

- 541 • ever had a severe allergic (hypersensitivity) reaction to TYKERB. Check with your doctor if  
542 you think this applies to you. Don't take TYKERB.
- 543 • have heart problems.
- 544 • have liver problems. You may need a lower dose of TYKERB.
- 545 • are pregnant or may become pregnant. TYKERB may harm an unborn baby. If you become  
546 pregnant during treatment with TYKERB, tell your doctor as soon as possible.
- 547 • are breast-feeding. It is not known if TYKERB passes into your breast milk or if it can harm  
548 your baby. If you are a woman who has or will have a baby, talk with your doctor about the  
549 best way to feed your baby.

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

- 555
- 556 Especially tell your doctor if you take:
- 557 • antibiotics and anti-fungals (drugs used to treat infections)
  - 558 • HIV (AIDS) treatments
  - 559 • anticonvulsant drugs (drugs used to treat seizures)
  - 560 • calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
  - 561 • antidepressants
  - 562 • drugs used for stomach ulcers
  - 563 • St. John's Wort or other herbal supplements
- 564

565 Know the medicines you take. Keep a list of your medicines with you to show your doctor. Do  
566 not take other medicines during treatment with TYKERB without first checking with your  
567 doctor.

568

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

571

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

- 573 • Take TYKERB exactly as your doctor tells you to take it. Your doctor may change your dose  
574 of TYKERB if needed.
    - 575 • For patients with advanced or metastatic breast cancer, TYKERB and capecitabine are  
576 taken in 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by  
577 mouth all at once, **one time a day on days 1 to 21**. Your doctor will tell you the dose of  
578 capecitabine you should take and when you should take it.
    - 579 • For patients with hormone receptor positive, HER2 positive breast cancer, TYKERB and  
580 letrozole are taken daily. The usual dose of TYKERB is 1,500 mg (6 tablets) taken by  
581 mouth all at once, **one time a day**. Your doctor will tell you the dose of letrozole you  
582 should take and when you should take it.
  - 583 • TYKERB should be taken at least one hour before, or at least one hour after food.
  - 584 • Do not eat or drink grapefruit products while taking TYKERB.
  - 585 • If you forget to take your dose of TYKERB, do not take two doses at one time. Take your  
586 next dose at your scheduled time.
- 587

### 588 **What are the possible side effects of TYKERB?**

589 **Serious side effects** include:

- 590 • **heart problems** including, decreased pumping of blood from the heart and an abnormal  
591 heartbeat. Signs and symptoms of an abnormal heartbeat include:
  - 592 • feeling like your heart is pounding or racing
  - 593 • dizziness
  - 594 • tiredness
  - 595 • feeling lightheaded
  - 596 • shortness of breath
    - 597 • Your doctor should check your heart function before you start taking TYKERB and  
598 during treatment.
- 599 • **liver problems.** Signs and symptoms of liver problems include:
  - 600 • itching
  - 601 • yellow eyes or skin
  - 602 • dark urine
  - 603 • pain or discomfort in the right upper stomach area
  - 604 • death
    - 605 • Your doctor should do blood tests to check your liver before you start taking  
606 TYKERB and during treatment.
- 607 • **diarrhea**, which may cause you to become dehydrated. Follow your doctors instructions for  
608 what to do to help prevent or treat diarrhea.
- 609 • **lung problems.** Symptoms of a lung problem with TYKERB include a cough that will not  
610 go away or shortness of breath.

611  
612 **Call your doctor right away if you have any of the signs or symptoms of the serious side**  
613 **effects listed above.**

614  
615 **Common side effects** of TYKERB in combination with capecitabine or letrozole include:

- 616 • diarrhea
- 617 • red, painful hands and feet
- 618 • nausea
- 619 • rash
- 620 • vomiting
- 621 • tiredness or weakness
- 622 • mouth sores
- 623 • loss of appetite
- 624 • indigestion
- 625 • unusual hair loss or thinning
- 626 • nose bleeds
- 627 • headache
- 628 • dry skin
- 629 • itching

630 • nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles.

631

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

633

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

636

637 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
638 1-800-FDA-1088.

639

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

642

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

644 • Store TYKERB tablets at room temperature at 59° to 86°F (15° to 30°C). Keep the  
645 container closed tightly.

646 • Do not keep medicine that is out of date or that you no longer need. Be sure that if you  
647 throw any medicine away, it is out of the reach of children.

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

649

#### 650 **General information about TYKERB**

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

655

656 This leaflet summarizes the most important information about TYKERB. If you would like more  
657 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
658 TYKERB that is written for health professionals. For more information, you can call toll-free 1-  
659 888-825-5249 or by visiting the website [www.tykerb.com](http://www.tykerb.com).

660

#### 661 **What are the ingredients in TYKERB?**

662 **Active Ingredient:** Lapatinib.

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

666

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

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671 TYKERB is a registered trademark of GlaxoSmithKline.

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674 GlaxoSmithKline

675 Research Triangle Park, NC 27709

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