

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).]

-----**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/m²/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)

-----**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.

-----**DRUG INTERACTIONS**-----

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

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

Revised: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosing
- 2.2 Dose Modification Guidelines

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Decreased Left Ventricular Ejection Fraction
- 5.2 Hepatotoxicity
- 5.3 Patients with Severe Hepatic Impairment
- 5.4 Diarrhea
- 5.5 Interstitial Lung Disease/Pneumonitis
- 5.6 QT Prolongation
- 5.7 Use in Pregnancy

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems
- 7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes
- 7.3 Drugs that Inhibit Drug Transport Systems
- 7.4 Acid Reducing Agents

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 QT Prolongation

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 HER2 Positive Metastatic Breast Cancer
- 14.2 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Information for Patients
- 17.2 FDA-Approved Patient Labeling

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

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[®] 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/m²/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 ² /day (N = 198)			Capecitabine 2,500 mg/m ² /day (N = 191)		
	All Grades ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash ^b	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

155

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

156

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

160 ^a 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 ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
	%	%	%	%	%	%
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Anorexia	11	<1	0	9	<1	0
Skin and subcutaneous tissue disorders						
Rash ^b	44	1	0	13	0	0
Dry skin	13	<1	0	4	0	0
Alopecia	13	<1	0	7	0	0
Pruritus	12	<1	0	9	<1	0
Nail Disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Respiratory, thoracic, and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0

172 ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

173 ^b 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 ^a	Grade 3	Grade 4	All Grades ^a	Grade 3	Grade 4
Hepatic Parameters	%	%	%	%	%	%
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0
Total Bilirubin	22	<1	<1	11	1	<1

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

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

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

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

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

224 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

230 **Ketoconazole:** In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at
231 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to
232 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

233 **Carbamazepine:** In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at
234 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to
235 lapatinib was decreased approximately 72%.

236 **7.3 Drugs that Inhibit Drug Transport Systems**

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

240 **7.4 Acid Reducing Agents**

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

245 **8 USE IN SPECIFIC POPULATIONS**

246 **8.1 Pregnancy**

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

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

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

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

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

272 **8.3 Nursing Mothers**

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

277 **8.4 Pediatric Use**

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

279 **8.5 Geriatric Use**

280 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in
281 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were
282 75 years of age and older. Of the total number of hormone receptor positive, HER2 positive
283 metastatic breast cancer patients in clinical studies of TYKERB in combination with letrozole
284 (N = 642), 44% were 65 years of age and older, and 12% were 75 years of age and older. No
285 overall differences in safety or effectiveness were observed between elderly subjects and
286 younger subjects, and other reported clinical experience has not identified differences in
287 responses between the elderly and younger patients, but greater sensitivity of some older
288 individuals cannot be ruled out.

289 **8.6 Renal Impairment**

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

295 **8.7 Hepatic Impairment**

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

306 **10 OVERDOSAGE**

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

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

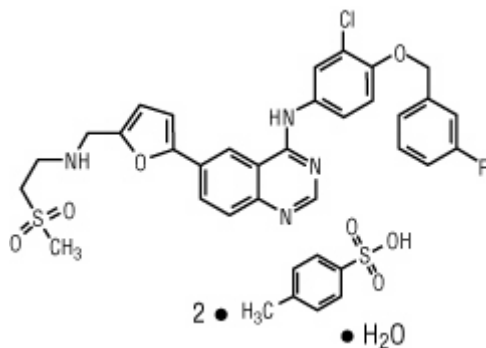
317 Because lapatinib is not significantly renally excreted and is highly bound to plasma
318 proteins, hemodialysis would not be expected to be an effective method to enhance the
319 elimination of lapatinib.

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

321 **11 DESCRIPTION**

322 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase
323 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-
324 chloro-4-[[3-fluorophenyl)methyl]oxy]phenyl)-6-[5-({2-
325 (methylsulfonyl)ethyl}amino)methyl]-2-furanyl]-4-quinazolinamine bis(4-
326 methylbenzenesulfonate) monohydrate. It has the molecular formula C₂₉H₂₆ClFN₄O₄S
327 (C₇H₈O₃S)₂ H₂O and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the

328 following chemical structure:



329

330 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is
331 0.001 mg/mL at 25°C.

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

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

338 12 CLINICAL PHARMACOLOGY

339 12.1 Mechanism of Action

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

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

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

355 12.3 Pharmacokinetics

356 **Absorption:** Absorption following oral administration of TYKERB is incomplete and
357 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to
358 1.5 hour). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours

359 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to
360 7 days, indicating an effective half-life of 24 hours.

361 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)
362 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
363 to 56 mcg.hr/mL).

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

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

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

375 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and
376 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated
377 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or
378 10% of lapatinib concentration in plasma.

379 Elimination: At clinical doses, the terminal phase half-life following a single dose was
380 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

381 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with
382 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of
383 27% (range 3 to 67%) of an oral dose.

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

386 **12.4 QT Prolongation**

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

392 **13 NONCLINICAL TOXICOLOGY**

393 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

394 Two-year carcinogenicity studies with lapatinib are ongoing.

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

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

400 There were no effects on male or female rat mating or fertility at doses up to
401 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times
402 the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus
403 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,
404 when female rats were given oral doses of lapatinib during breeding and through the first 6 days
405 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and
406 in the fetal body weights at ≥ 60 mg/kg/day (approximately 6.4 times and 3.3 times the expected
407 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine,
408 respectively).

409 **14 CLINICAL STUDIES**

410 **14.1 HER2 Positive Metastatic Breast Cancer**

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

416 Patients were randomized to receive either TYKERB 1,250 mg once daily (continuously)
417 plus capecitabine 2,000 mg/m²/day on Days 1-14 every 21 days, or to receive capecitabine alone
418 at a dose of 2,500 mg/m²/day on Days 1-14 every 21 days. The endpoint was time to progression
419 (TTP). TTP was defined as time from randomization to tumor progression or death related to
420 breast cancer. Based on the results of a pre-specified interim analysis, further enrollment was
421 discontinued. Three hundred and ninety-nine (399) patients were enrolled in this study. The
422 median age was 53 years and 14% were older than 65 years. Ninety-one percent (91%) were
423 Caucasian. Ninety-seven percent (97%) had stage IV breast cancer, 48% were estrogen receptor+
424 (ER+) or progesterone receptor+ (PR+), and 95% were ErbB2 IHC 3+ or IHC 2+ with FISH
425 confirmation. Approximately 95% of patients had prior treatment with anthracyclines, taxanes,
426 and trastuzumab.

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

429

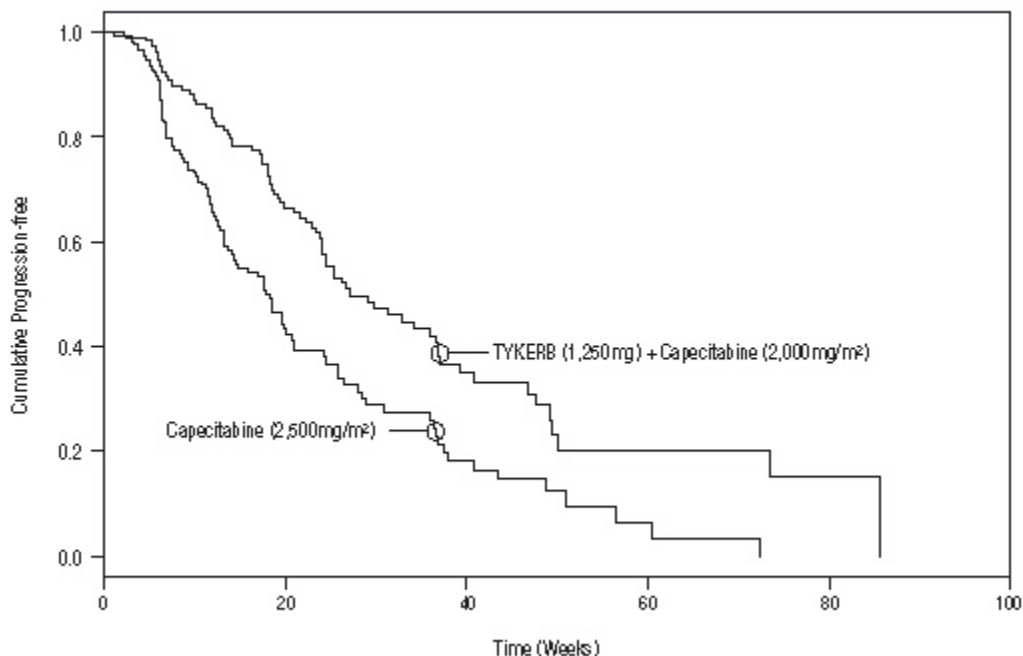
430 **Table 5. Efficacy Results**

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

431 TTP = Time to progression.

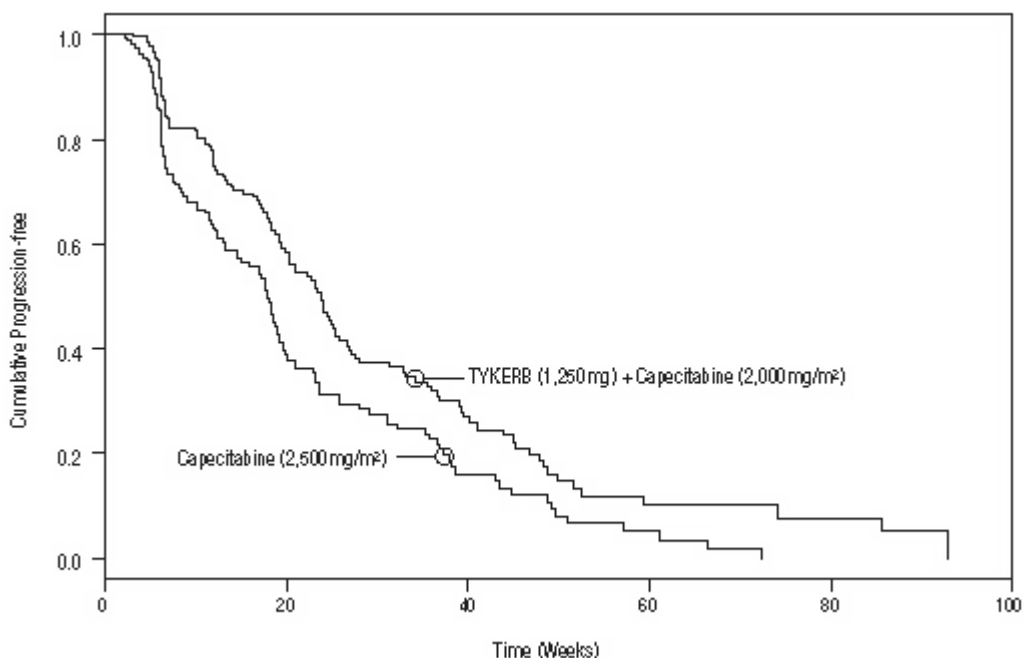
432 ^a The time from last tumor assessment to the data cut-off date was >100 days in approximately
 433 30% of patients in the independent assessment. The pre-specified assessment interval was 42 or
 434 84 days.

435
 436 **Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to**
 437 **Progression**



438
 439

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



441
442

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

448

449 **Table 6: Overall Survival Data**

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m²/day (N = 207)	Capecitabine 2,500 mg/m²/day (N = 201)
Overall Survival		
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	

450 CI = confidence interval

451

452 **14.2 Hormone Receptor Positive, HER2 Positive Metastatic Breast Cancer**

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

454 double-blind, placebo-controlled, multi-center study. A total of 1,286 postmenopausal women
 455 with hormone receptor positive (ER positive and/or PgR positive) metastatic breast cancer, who
 456 had not received prior therapy for metastatic disease, were randomly assigned to receive either
 457 TYKERB (1,500 mg once daily) plus letrozole (2.5 mg once daily) (n = 642) or letrozole (2.5 mg
 458 once daily) alone (n = 644). Of all patients randomized to treatment, 219 (17%) patients had
 459 tumors overexpressing the HER2 receptor, defined as fluorescence in situ hybridization (FISH)
 460 ≥ 2 or 3+ immunohistochemistry (IHC). There were 952 (74%) patients who were HER2 negative
 461 and 115 (9%) patients did not have their HER2 receptor status confirmed. The primary objective
 462 was to evaluate and compare progression-free survival (PFS) in the HER2 positive population.
 463 Progression-free survival was defined as the interval of time between date of randomization and
 464 the earlier date of first documented sign of disease progression or death due to any cause.

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

470 In the HER2 positive subgroup (n = 219), the addition of TYKERB to letrozole resulted
 471 in an improvement in PFS. In the HER2 negative subgroup, there was no improvement in PFS of
 472 the TYKERB plus letrozole combination compared to the letrozole plus placebo. Overall
 473 response rate (ORR) was also improved with the TYKERB plus letrozole combination therapy.
 474 The overall survival (OS) data were not mature. Efficacy analyses for the hormone receptor
 475 positive, HER2 positive and HER2 negative subgroups are presented in Table 7 and Figure 3.
 476

477

Table 7. Efficacy Results

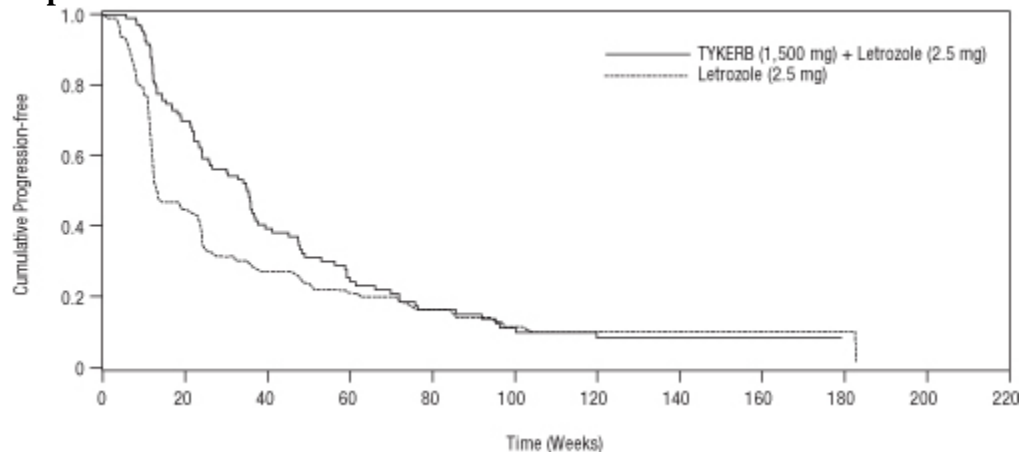
	HER2(+) Population		HER2(-) Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
Median PFS^a, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9,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

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

479 ^a Kaplan-Meier estimate.

480

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



483
484

485 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

491 **17 PATIENT COUNSELING INFORMATION**

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

493 **17.1 Information for Patients**

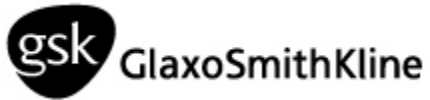
494 Patients should be informed of the following:

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

510 **17.2 FDA-Approved Patient Labeling**

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

513
514 TYKERB is a registered trademark of GlaxoSmithKline.
515



516
517 GlaxoSmithKline
518 Research Triangle Park, NC 27709
519
520 ©YEAR, GlaxoSmithKline. All rights reserved.
521
522 Month YEAR
523 TKB:XPI

527 **PATIENT INFORMATION**
528

529 **TYKERB (TIE-curb)**
530 **(lapatinib) tablets**
531

532 Read this leaflet before you start taking TYKERB[®] and each time you get a refill. There may be
533 new information. This information does not take the place of talking with your doctor about your
534 medical condition or treatment.
535

536 **What is TYKERB?**

537 TYKERB is used with the medicine capecitabine for the treatment of patients with advanced or
538 metastatic breast cancer that is HER2 positive (tumors that produce large amounts of a protein
539 called human epidermal growth factor receptor-2), and who have already had certain other breast
540 cancer treatments.
541

542 TYKERB is also used with a type of medicine called letrozole for the treatment of
543 postmenopausal women with hormone receptor positive, HER2 positive metastatic breast cancer
544 for whom hormonal therapy is indicated. TYKERB in combination with an aromatase inhibitor
545 has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of
546 metastatic breast cancer.
547

548 **Who should not take TYKERB?**

549 Do not take TYKERB if you are allergic to any of its ingredients. See the end of this leaflet for a
550 list of ingredients in TYKERB.
551

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

- 554 • ever had a severe allergic (hypersensitivity) reaction to TYKERB. Check with your doctor if
555 you think this applies to you. Don't take TYKERB.
- 556 • have heart problems.
- 557 • have liver problems. You may need a lower dose of TYKERB.
- 558 • are pregnant or may become pregnant. TYKERB may harm an unborn baby. If you become
559 pregnant during treatment with TYKERB, tell your doctor as soon as possible.
- 560 • are breast-feeding. It is not known if TYKERB passes into your breast milk or if it can harm
561 your baby. If you are a woman who has or will have a baby, talk with your doctor about the
562 best way to feed your baby.
563

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

568

569 Especially tell your doctor if you take:

- 570 • antibiotics and anti-fungals (drugs used to treat infections)
- 571 • HIV (AIDS) treatments
- 572 • anticonvulsant drugs (drugs used to treat seizures)
- 573 • calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- 574 • antidepressants
- 575 • drugs that decrease stomach acidity
- 576 • St. John's Wort or other herbal supplements

577

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

581

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

584

585 **How should I take TYKERB?**

- 586 • Take TYKERB exactly as your doctor tells you to take it. Your doctor may change your
587 dose of TYKERB if needed.
- 588 • For patients with advanced or metastatic breast cancer, TYKERB and capecitabine are
589 taken in 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by
590 mouth all at once, **one time a day on days 1 to 21**. Your doctor will tell you the dose of
591 capecitabine you should take and when you should take it.
- 592 • For patients with hormone receptor positive, HER2 positive breast cancer, TYKERB and
593 letrozole are taken daily. The usual dose of TYKERB is 1,500 mg (6 tablets) taken by
594 mouth all at once, **one time a day**. Your doctor will tell you the dose of letrozole you
595 should take and when you should take it.
- 596 • TYKERB should be taken at least one hour before, or at least one hour after food.
- 597 • Do not eat or drink grapefruit products while taking TYKERB.
- 598 • If you forget to take your dose of TYKERB, do not take two doses at one time. Take your
599 next dose at your scheduled time.
- 600 • If you take too much TYKERB, call your doctor or poison control center, or go to the
601 nearest hospital emergency room right away. Take TYKERB tablets with you when
602 possible.

603

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

605 **Serious side effects** include:

- 606 • **heart problems** including, decreased pumping of blood from the heart and an abnormal
607 heartbeat. Signs and symptoms of an abnormal heartbeat include:
- 608 • feeling like your heart is pounding or racing
 - 609 • dizziness
 - 610 • tiredness
 - 611 • feeling lightheaded
 - 612 • shortness of breath
 - 613 • Your doctor should check your heart function before you start taking TYKERB and
614 during treatment.
- 615 • **liver problems.** Signs and symptoms of liver problems include:
- 616 • itching
 - 617 • yellow eyes or skin
 - 618 • dark urine
 - 619 • pain or discomfort in the right upper stomach area
 - 620 • death
 - 621 • Your doctor should do blood tests to check your liver before you start taking
622 TYKERB and during treatment.
- 623 • **diarrhea**, which may cause you to become dehydrated. Follow your doctors instructions for
624 what to do to help prevent or treat diarrhea.
- 625 • **lung problems.** Symptoms of a lung problem with TYKERB include a cough that will not
626 go away or shortness of breath.
- 627

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

630

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

- 632 • diarrhea
- 633 • red, painful hands and feet
- 634 • nausea
- 635 • rash
- 636 • vomiting
- 637 • tiredness or weakness
- 638 • mouth sores
- 639 • loss of appetite
- 640 • indigestion
- 641 • unusual hair loss or thinning
- 642 • nose bleeds
- 643 • headache

- 644 • dry skin
645 • itching
646 • nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles.
647

648 Tell your doctor about any side effect that gets serious or that does not go away.
649

650 These are not all the side effects with TYKERB. Ask your doctor or pharmacist for more
651 information.
652

653 Call your doctor for medical advice about side effects. You may report side effects to FDA at
654 1-800-FDA-1088.
655

656 **You may also get side effects from the other drugs taken with TYKERB.** Talk to your doctor
657 about possible side effects you may get during treatment.
658

659 **How should I store TYKERB tablets?**

- 660 • Store TYKERB tablets at room temperature at 59° to 86°F (15° to 30°C). Keep the
661 container closed tightly.
662 • Do not keep medicine that is out of date or that you no longer need. Be sure that if you
663 throw any medicine away, it is out of the reach of children.
664 • **Keep TYKERB and all medicines out of the reach of children.**
665

666 **General information about TYKERB**

667 Medicines are sometimes prescribed for conditions that are not mentioned in patient information
668 leaflets. Do not use TYKERB for any other condition for which it was not prescribed. Do not
669 give TYKERB to other people, even if they have the same condition that you have. It may harm
670 them.
671

672 This leaflet summarizes the most important information about TYKERB. If you would like more
673 information, talk with your doctor. You can ask your doctor or pharmacist for information about
674 TYKERB that is written for health professionals. For more information, you can call toll-free 1-
675 888-825-5249 or by visiting the website www.tykerb.com.
676

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

678 **Active Ingredient:** Lapatinib.

679 **Inactive Ingredients: Tablet Core:** Magnesium stearate, microcrystalline cellulose, povidone,
680 sodium starch glycolate. **Coating:** Orange film-coat: FD&C yellow #6/sunset yellow FCF
681 aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.
682

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



684

685

686 TYKERB is a registered trademark of GlaxoSmithKline.

687



688

689 GlaxoSmithKline

690 Research Triangle Park, NC 27709

691

692 ©YEAR, GlaxoSmithKline. All rights reserved.

693

694 Revised: Month YEAR

695 TKB:XPIL