

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYKERB safely and effectively. See full prescribing information for TYKERB.

TYKERB (lapatinib) tablets, for oral use
Initial U.S. Approval: 2007

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.
Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain [see Warnings and Precautions (5.2)].

RECENT MAJOR CHANGES

Indication and Usage (1)	10/2013
Dosage and Administration, Dose Modification Guidelines (2.2)	12/2012
Warnings and Precautions, Diarrhea (5.4)	06/2013

INDICATIONS AND USAGE

TYKERB, a kinase inhibitor, is indicated in combination with: (1)

- capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
Limitation of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB in combination with capecitabine.
- letrozole for the treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

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

DOSAGE AND ADMINISTRATION

The recommended dosage of TYKERB for advanced or metastatic breast cancer is 1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/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 1,500 mg (6 tablets) given orally once daily continuously in combination with letrozole. When TYKERB is coadministered with letrozole, the recommended dose of letrozole is 2.5 mg once daily. (2.1)

- TYKERB should be taken at least one hour before or one hour after a meal. However, capecitabine should be taken with food or within 30 minutes after food. (2.1)
- TYKERB should be taken once daily. Do not divide daily doses of TYKERB. (2.1, 12.3)
- Modify dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions. (2.2)

DOSAGE FORMS AND STRENGTHS

250 mg tablets (3)

CONTRAINDICATIONS

Known severe hypersensitivity (e.g., anaphylaxis) to this product or any of its components. (4)

WARNINGS AND PRECAUTIONS

- Decreases in left ventricular ejection fraction (LVEF) have been reported. Confirm normal LVEF before starting TYKERB and continue evaluations during treatment. (5.1)
- Lapatinib has been associated with hepatotoxicity. Monitor liver function tests before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. Discontinue and do not restart TYKERB if patients experience severe changes in liver function tests. (5.2)
- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.3, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.4)
- Lapatinib has been associated with interstitial lung disease and pneumonitis. Discontinue TYKERB if patients experience severe pulmonary symptoms. (5.5)
- Lapatinib may prolong the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.6, 12.4)
- 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: 10/2013

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: HEPATOTOXICITY**

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

6 **1 INDICATIONS AND USAGE**

7 TYKERB[®] 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,
10 a taxane, and trastuzumab.

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

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

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

18 **2 DOSAGE AND ADMINISTRATION**

19 **2.1 Recommended Dosing**

20 HER2-Positive Metastatic Breast Cancer: The recommended dose of TYKERB is
21 1,250 mg given orally once daily on Days 1-21 continuously in combination with capecitabine
22 2,000 mg/m²/day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in
23 a repeating 21-day cycle. TYKERB should be taken at least one hour before or one hour after a
24 meal. The dose of TYKERB should be once daily (5 tablets administered all at once); dividing
25 the daily dose is not recommended [see *Clinical Pharmacology (12.3)*]. Capecitabine should be
26 taken with food or within 30 minutes after food. If a day's dose is missed, the patient should not
27 double the dose the next day. Treatment should be continued until disease progression or
28 unacceptable toxicity occurs.

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

35 **2.2 Dose Modification Guidelines**

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

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

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

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

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

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

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

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

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

89 **3 DOSAGE FORMS AND STRENGTHS**

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

92 **4 CONTRAINDICATIONS**

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

95 **5 WARNINGS AND PRECAUTIONS**

96 **5.1 Decreased Left Ventricular Ejection Fraction**

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

105 **5.2 Hepatotoxicity**

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

114 **5.3 Patients With Severe Hepatic Impairment**

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

120 **5.4 Diarrhea**

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

133 **5.5 Interstitial Lung Disease/Pneumonitis**

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

139 **5.6 QT Prolongation**

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

147 **5.7 Use in Pregnancy**

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

152 There are no adequate and well-controlled studies with TYKERB in pregnant women.
153 Women should be advised not to become pregnant when taking TYKERB. If this drug is used

154 during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be
155 apprised of the potential hazard to the fetus.

156 **6 ADVERSE REACTIONS**

157 **6.1 Clinical Trials Experience**

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

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

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

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

172

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

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day (N = 198)			Capecitabine 2,500 mg/m ² /day (N = 191)		
Reactions	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

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

175 ^b Grade 3 dermatitis acneiform was reported in <1% of patients in the group receiving
176 TYKERB plus capecitabine.

177

178 **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

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

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

189

190 **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

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

192 ^b In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional
 193 subjects in each treatment arm had rash under "Infections and infestations"; none were Grade
 194 3 or 4.

195

196 **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

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

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

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

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

214 **6.2 Postmarketing Experience**

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

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

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

222 **7 DRUG INTERACTIONS**

223 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport** 224 **Systems**

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

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

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

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

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

243 **7.2 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

249 **Ketoconazole:** In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at
250 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to
251 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

252 **Carbamazepine:** In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at
253 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to
254 lapatinib was decreased approximately 72%.

255 **7.3 Drugs That Inhibit Drug Transport Systems**

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

259 **7.4 Acid-Reducing Agents**

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

264 **8 USE IN SPECIFIC POPULATIONS**

265 **8.1 Pregnancy**

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

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

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

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

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

291 **8.3 Nursing Mothers**

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

296 **8.4 Pediatric Use**

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

298 **8.5 Geriatric Use**

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

308 **8.6 Renal Impairment**

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

314 **8.7 Hepatic Impairment**

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

325 **10 OVERDOSAGE**

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

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

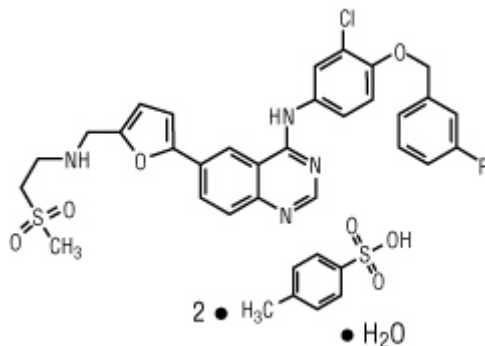
336 Because lapatinib is not significantly renally excreted and is highly bound to plasma
337 proteins, hemodialysis would not be expected to be an effective method to enhance the
338 elimination of lapatinib.

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

340 **11 DESCRIPTION**

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

347 following chemical structure:



349 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is
350 0.001 mg/mL at 25°C.

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

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

357 12 CLINICAL PHARMACOLOGY

358 12.1 Mechanism of Action

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

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

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

374 12.3 Pharmacokinetics

375 **Absorption:** Absorption following oral administration of TYKERB is incomplete and
376 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to
377 1.5 hours). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours

378 after administration. Daily dosing of TYKERB results in achievement of steady-state within 6 to
379 7 days, indicating an effective half-life of 24 hours.

380 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)
381 values of C_{max} were 2.43 mcg/mL (1.57 to 3.77 mcg/mL) and AUC were 36.2 mcg.h/mL (23.4 to
382 56 mcg.h/mL).

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

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

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

394 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and
395 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated
396 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or
397 10% of lapatinib concentration in plasma.

398 Elimination: At clinical doses, the terminal phase half-life following a single dose was
399 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

400 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with
401 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of
402 27% (range 3% to 67%) of an oral dose.

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

405 **12.4 QT Prolongation**

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

411 **12.5 Pharmacogenomics**

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

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

420 **13 NONCLINICAL TOXICOLOGY**

421 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

422 Two-year carcinogenicity studies with lapatinib are ongoing.

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

428 There were no effects on male or female rat mating or fertility at doses up to
429 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times
430 the expected human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus
431 capecitabine, respectively). The effect of lapatinib on human fertility is unknown. However,
432 when female rats were given oral doses of lapatinib during breeding and through the first 6 days
433 of gestation, a significant decrease in the number of live fetuses was seen at 120 mg/kg/day and
434 in the fetal body weights at ≥ 60 mg/kg/day (approximately 6.4 times and 3.3 times the expected
435 human clinical exposure based on AUC following 1,250 mg dose of lapatinib plus capecitabine,
436 respectively).

437 **14 CLINICAL STUDIES**

438 **14.1 HER2-Positive Metastatic Breast Cancer**

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

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

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

457

458 **Table 5. Efficacy Results**

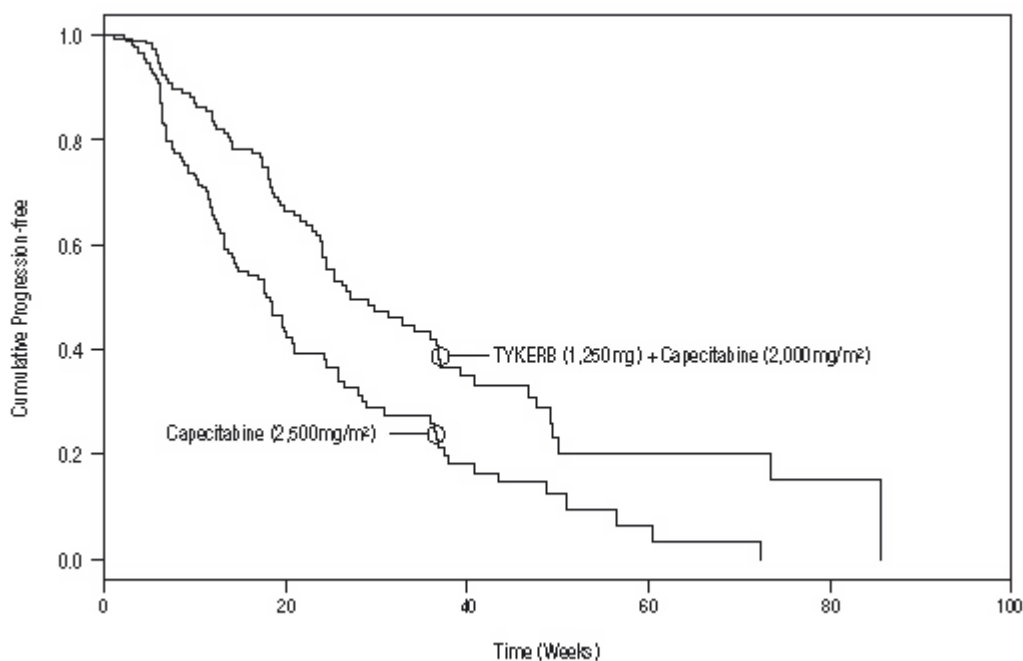
	Independent Assessment ^a		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
Number of TTP events	82	102	121	126
Median 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 (HR) (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)

459 TTP = Time to progression.

460 ^a The time from last tumor assessment to the data cut-off date was >100 days in approximately
461 30% of patients in the independent assessment. The pre-specified assessment interval was 42
462 or 84 days.

463

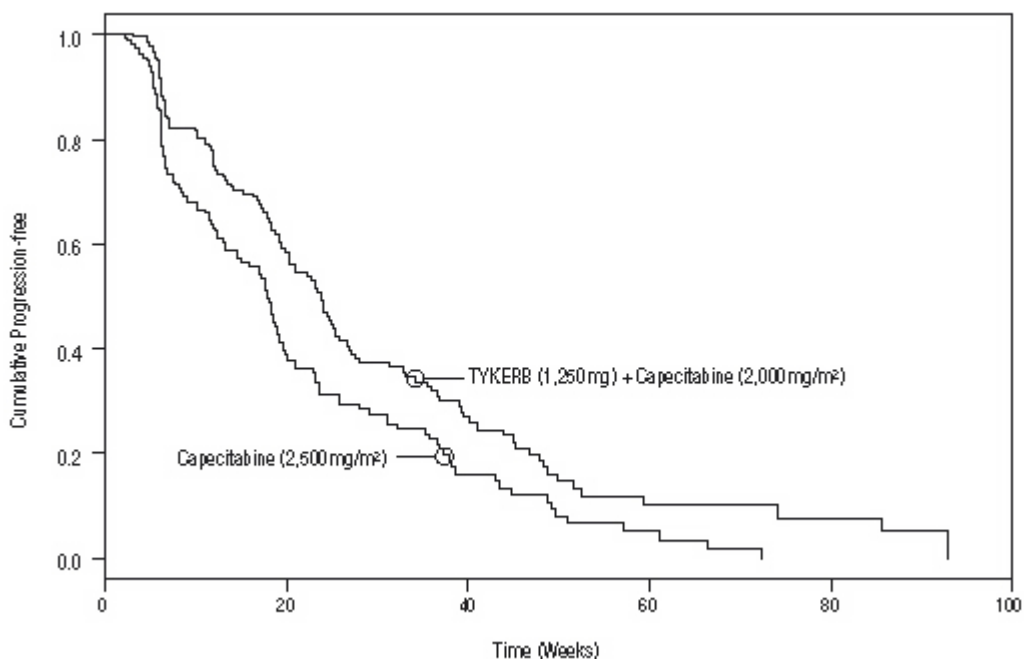
464 **Figure 1. Kaplan-Meier Estimates for Independent Review Panel-evaluated Time to**
465 **Progression**



466

467
468

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



469
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At the time of above efficacy analysis, the overall survival data were not mature (32% events). However, based on the TTP results, the study was unblinded and patients receiving capecitabine alone were allowed to cross over to treatment with TYKERB plus capecitabine. The survival data were followed for an additional 2 years to be mature and the analysis is summarized in Table 6.

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	

478
479
480

CI = confidence interval.

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

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

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

499 **14.2 Hormone Receptor Positive, HER2-Positive Metastatic Breast Cancer**

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

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

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

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

524

525 **Table 7. Efficacy Results**

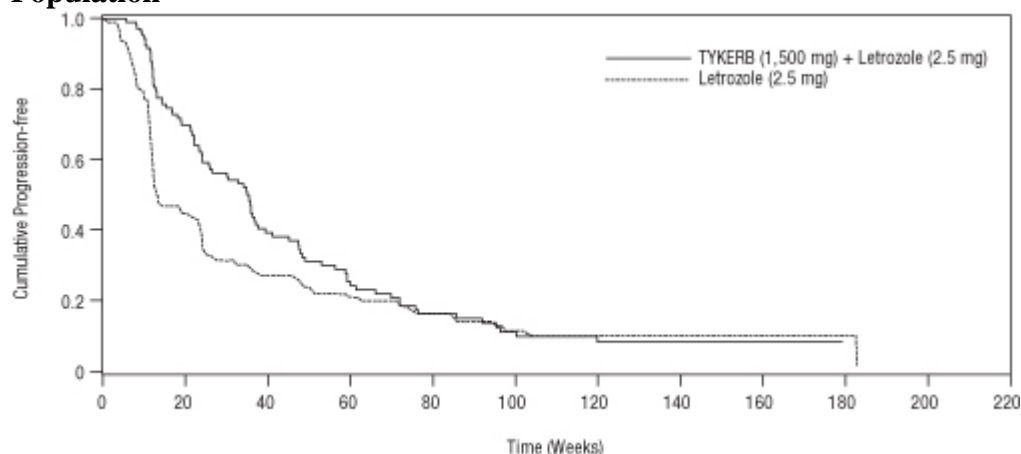
	HER2-Positive Population		HER2-Negative Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	Letrozole 2.5 mg/day
	(N = 111)	(N = 108)	(N = 478)	(N = 474)
Median PFS^a, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	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)

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

527 ^a Kaplan-Meier estimate.

528

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



531
 532

533 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

539 **17 PATIENT COUNSELING INFORMATION**
540 *See FDA-approved patient labeling (Patient Information).*

541 **17.1 Information for Patients**

542 Patients should be informed of the following:

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

558

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

560



561

562 GlaxoSmithKline

563 Research Triangle Park, NC 27709

564

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566

567 TKB:XXPI

571 **PATIENT INFORMATION**
572

573 **TYKERB® (TIE-curb)**
574 **(lapatinib)**
575 **tablets**
576

577 Read this leaflet before you start taking TYKERB and each time you get a refill.
578 There may be new information. This information does not take the place of talking
579 with your doctor about your medical condition or treatment.
580

581 **What is TYKERB?**

582 TYKERB is used with the medicine capecitabine for the treatment of people with
583 advanced or metastatic breast cancer that is HER2-positive (tumors that produce
584 large amounts of a protein called human epidermal growth factor receptor-2), and
585 who have already had certain other breast cancer treatments.
586

587 TYKERB is also used with a type of medicine called letrozole for the treatment of
588 postmenopausal women with hormone receptor-positive, HER2-positive metastatic
589 breast cancer for whom hormonal therapy is indicated.
590

591 It is not known if TYKERB is safe and effective in children.
592

593 **Who should not take TYKERB?**

594 Do not take TYKERB if you are allergic to any of the ingredients in TYKERB. See the
595 end of this leaflet for a complete list of ingredients in TYKERB.
596

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

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

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

608

609 **Tell your doctor about all the medicines you take**, including prescription and
610 over-the-counter medicines, vitamins, and herbal supplements. TYKERB may affect
611 the way other medicines work, and other medicines may affect the way TYKERB
612 works.

613

614 Especially tell your doctor if you take:

- 615 • antibiotics and anti-fungal medicines (used to treat infections)
- 616 • HIV medicines
- 617 • medicines used to treat seizures
- 618 • medicines used to treat heart problems or high blood pressure
- 619 • antidepressants
- 620 • medicines that reduce stomach acid (antacids)
- 621 • St. John's wort

622

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

626

627 **How should I take TYKERB?**

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

648

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

650 **TYKERB may cause serious side effects**, including:

- 651 • **heart problems**, including decreased pumping of blood from the heart and an
652 abnormal heartbeat. Signs and symptoms of an abnormal heartbeat include:
653 • feeling like your heart is pounding or racing
654 • dizziness
655 • tiredness
656 • feeling lightheaded
657 • shortness of breath

658 Your doctor should check your heart function before you start taking TYKERB
659 and during treatment.

- 660 • **liver problems**. Liver problems can be severe and deaths have happened.
661 Signs and symptoms of liver problems include:

- 662 • itching
663 • yellowing of your skin or the white part of your eyes
664 • dark urine
665 • pain or discomfort in the right upper stomach area

666 Your doctor should do blood tests to check your liver before you start taking
667 TYKERB and during treatment.

- 668 • **diarrhea**. Diarrhea is common with TYKERB and may sometimes be severe.
669 Severe diarrhea can cause loss of body fluid (dehydration) and some deaths
670 have happened. Call your doctor right away if you have a change in bowel
671 pattern or if you have severe diarrhea. Follow your doctor's instructions for
672 what to do to help prevent or treat diarrhea.

- 673 • **lung problems**. Symptoms of a lung problem with TYKERB include a cough
674 that will not go away or shortness of breath.

675

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

678

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

- 681 • diarrhea
682 • red, painful hands and feet
683 • nausea
684 • rash
685 • vomiting
686 • tiredness or weakness
687 • mouth sores

- 688 • loss of appetite
- 689 • indigestion
- 690 • unusual hair loss or thinning
- 691 • nose bleeds
- 692 • headache
- 693 • dry skin
- 694 • itching
- 695 • nail disorders such as nail bed changes, nail pain, infection and swelling of the
- 696 cuticles.

697

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

700

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

703

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

706

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

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

709

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

- 711 • Store TYKERB Tablets at room temperature between 68° and 77°F (20° and
- 712 25°C).
- 713 • Keep the container closed tightly.
- 714 • Do not keep medicine that is out of date or that you no longer need.

715

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

717

718 **General information about TYKERB**

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

723

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

727

728 For more information, call 1-888-825-5249 or go to www.tykerb.com.

729

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

731 **Active ingredient:** Lapatinib.

732 **Inactive ingredients: Tablet Core:** Magnesium stearate, microcrystalline
733 cellulose, povidone, sodium starch glycolate. **Coating:** Orange film-coat: FD&C
734 yellow No. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400,
735 polysorbate 80, titanium dioxide.

736

737 This Patient Information has been approved by the U.S. Food and Drug
738 Administration.

739

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

741



742

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