

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

RECENT MAJOR CHANGES

Interstitial lung disease and pneumonitis. (5.4) Month YEAR

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

The recommended dosage of TYKERB 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)

- 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

None. (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)

- Dose reduction in patients with severe hepatic impairment should be considered. (2.2, 5.2, 8.7)
- Diarrhea, including severe diarrhea, has been reported during treatment. Manage with anti-diarrheal agents, and replace fluids and electrolytes if severe. (5.3)
- Lapatinib has been associated with interstitial lung disease and pneumonitis. Discontinue TYKERB if patients experience severe pulmonary symptoms. (5.4)
- Lapatinib prolongs the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.5)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.6)

ADVERSE REACTIONS

The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, 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 metabolized by CYP3A4 or CYP2C8. (7.1)
- Avoid strong CYP3A4 inhibitors. If unavoidable, consider dose reduction of TYKERB in patients coadministered a strong CYP3A4 inhibitor. (2.2, 7.2)
- Avoid strong CYP3A4 inducers. If unavoidable, consider gradual dose increase of TYKERB in patients coadministered a strong CYP3A4 inducer. (2.2, 7.2)

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

Revised: Month YEAR
TKB: XPI

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 TYKERB is indicated in combination with capecitabine for the treatment of patients with
4 advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received
5 prior therapy including an anthracycline, a taxane, and trastuzumab.

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Recommended Dosing**

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

16 **2.2 Dose Modification Guidelines**

17 Cardiac Events: TYKERB should be discontinued in patients with a decreased left
18 ventricular ejection fraction (LVEF) that is Grade 2 or greater by NCI Common Terminology
19 Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the
20 institution's lower limit of normal [*see Warnings and Precautions (5.1) and Adverse Reactions*
21 *(6.1)*]. TYKERB may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks
22 if the LVEF recovers to normal and the patient is asymptomatic.

23 Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh Class C)
24 should have their dose of TYKERB reduced. A dose reduction to 750 mg/day in patients with
25 severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal
26 range and should be considered. However, there is no clinical data with this dose adjustment in
27 patients with severe hepatic impairment.

28 Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4
29 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir,
30 indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit
31 may also increase plasma concentrations of lapatinib and should be avoided. If patients must be
32 coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction
33 to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without
34 inhibitors and should be considered. However, there are no clinical data with this dose
35 adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is

36 discontinued, a washout period of approximately 1 week should be allowed before the lapatinib
37 dose is adjusted upward to the indicated dose. [See Drug Interactions (7.2).]

38 **Concomitant Strong CYP3A4 Inducers:** The concomitant use of strong CYP3A4
39 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin,
40 rifapentin, phenobarbital, St. John's Wort). If patients must be coadministered a strong CYP3A4
41 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually
42 from 1,250 mg/day up to 4,500 mg/day based on tolerability. This dose of lapatinib is predicted
43 to adjust the lapatinib AUC to the range observed without inducers and should be considered.
44 However, there are no clinical data with this dose adjustment in patients receiving strong
45 CYP3A4 inducers. If the strong inducer is discontinued the lapatinib dose should be reduced to
46 the indicated dose. [See Drug Interactions (7.2).]

47 **Other Toxicities:** Discontinuation or interruption of dosing with TYKERB may be
48 considered when patients develop \geq Grade 2 NCI CTC toxicity and can be restarted at
49 1,250 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then
50 TYKERB should be restarted at a lower dose (1,000 mg/day).

51 **See manufacturer's prescribing information for capecitabine dosage adjustment**
52 **guidelines in the event of toxicity.**

53 **3 DOSAGE FORMS AND STRENGTHS**

54 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one
55 side.

56 **4 CONTRAINDICATIONS**

57 None.

58 **See manufacturer's prescribing information for capecitabine contraindications.**

59 **5 WARNINGS AND PRECAUTIONS**

60 **5.1 Decreased Left Ventricular Ejection Fraction**

61 TYKERB has been reported to decrease LVEF [see Adverse Reactions (6.1)]. In the
62 randomized clinical trial, the majority (>60%) of LVEF decreases occurred within the first 9
63 weeks of treatment; however, data on long-term exposure are limited. Caution should be taken if
64 TYKERB is to be administered to patients with conditions that could impair left ventricular
65 function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB
66 to ensure that the patient has a baseline LVEF that is within the institution's normal limits. LVEF
67 should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not
68 decline below the institution's normal limits [see Dosage and Administration (2.2)].

69 **5.2 Patients with Severe Hepatic Impairment**

70 If TYKERB is to be administered to patients with severe hepatic impairment, dose
71 reduction should be considered [see Dosage and Administration (2.2) and Use in Specific
72 Populations (8.7)].

73 **5.3 Diarrhea**

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

78 **5.4 Interstitial Lung Disease/Pneumonitis**

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

84 **5.5 QT Prolongation**

85 QT prolongation measured by automated machine-read evaluation of ECG was observed
86 in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients [see
87 *Clinical Pharmacology (12.4)*]. Lapatinib should be administered with caution to patients who
88 have or may develop prolongation of QTc. These conditions include patients with hypokalemia
89 or hypomagnesemia, with congenital long QT syndrome, patients taking anti-arrhythmic
90 medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose
91 anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to lapatinib
92 administration. The prescriber should consider baseline and on-treatment electrocardiograms
93 with QT measurement.

94 **5.6 Pregnancy**

95 Pregnancy Category D

96 TYKERB can cause fetal harm when administered to a pregnant woman. In a study
97 where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a
98 dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC),
99 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were
100 dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the
101 human clinical exposure based on AUC).

102 Lapatinib was studied for effects on embryo-fetal development in pregnant rats and
103 rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects;
104 however, minor anomalies (left-sided umbilical artery, cervical rib, and precocious ossification)
105 occurred in rats at the maternally toxic dose of 120 mg/kg/day (approximately 6.4 times the
106 human clinical exposure based on AUC). In rabbits, lapatinib was associated with maternal
107 toxicity at 60 and 120 mg/kg/day (approximately 0.07 and 0.2 times the human clinical exposure,
108 respectively, based on AUC) and abortions at 120 mg/kg/day. Maternal toxicity was associated
109 with decreased fetal body weights and minor skeletal variations.

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

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

114 **6 ADVERSE REACTIONS**

115 **6.1 Clinical Trials Experience**

116 The safety of TYKERB has been evaluated in more than 3,500 patients in clinical trials.
117 The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was
118 evaluated in 198 patients in a randomized, Phase 3 trial. [See *Clinical Studies (14)*.] Adverse
119 reactions which occurred in at least 10% of patients in either treatment arm and were higher in
120 the combination arm are shown in Table 1.

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

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

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

130

131 **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* %	Grade 3 %	Grade 4 %	All Grades* %	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 [†]	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

132 * National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

133 † Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine
134 group.

135

136 **Table 2. Selected Laboratory Abnormalities**

Parameters	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day			Capecitabine 2,500 mg/m ² /day		
	All Grades* %	Grade 3 %	Grade 4 %	All Grades* %	Grade 3 %	Grade 4 %
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

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

Decreases in Left Ventricular Ejection Fraction: Due to potential cardiac toxicity with HER2 (ErbB2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. LVEF decreases were defined as signs or symptoms of deterioration in left ventricular cardiac function that are ≥Grade 3 (NCI CTCAE), or a ≥20% decrease in left ventricular cardiac ejection fraction relative to baseline which is below the institution's lower limit of normal. Among 198 patients who received lapatinib/capecitabine combination treatment, 3 experienced Grade 2 and one had Grade 3 LVEF adverse reactions (NCI CTC 3.0). [See Warnings and Precautions (5.1).]

Interstitial Lung Disease/Pneumonitis: Lapatinib has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies [see Warnings and Precautions (5.4)].

7 DRUG INTERACTIONS

7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport Systems

Lapatinib inhibits CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP3A4 or CYP2C8. Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes in vitro, however, the clinical significance is unknown.

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

162 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

168 **Ketoconazole**: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at
169 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to
170 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

171 **Carbamazepine**: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at
172 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to
173 lapatinib was decreased approximately 72%.

174 **7.3 Drugs that Inhibit Drug Transport Systems**

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

178 **7.4 Other Chemotherapy Agents**

179 In a separate study, concomitant administration of lapatinib with capecitabine did not
180 meaningfully alter the pharmacokinetics of either agent (or the metabolites of capecitabine).

181 **8 USE IN SPECIFIC POPULATIONS**

182 **8.1 Pregnancy**

183 *Pregnancy Category D [see Warnings and Precautions (5.6)].*

184 **8.3 Nursing Mothers**

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

189 **8.4 Pediatric Use**

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

191 **8.5 Geriatric Use**

192 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in
193 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were
194 75 years of age and older. No overall differences in safety or effectiveness of the combination of
195 TYKERB and capecitabine were observed between these subjects and younger subjects, and
196 other reported clinical experience has not identified differences in responses between the elderly
197 and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

198 **8.6 Renal Impairment**

199 Lapatinib pharmacokinetics have not been specifically studied in patients with renal
200 impairment or in patients undergoing hemodialysis. There is no experience with TYKERB in

201 patients with severe renal impairment. However, renal impairment is unlikely to affect the
202 pharmacokinetics of lapatinib given that less than 2% (lapatinib and metabolites) of an
203 administered dose is eliminated by the kidneys.

204 **8.7 Hepatic Impairment**

205 The pharmacokinetics of lapatinib were examined in subjects with moderate (n = 8) or
206 severe (n = 4) hepatic impairment (Child-Pugh Class B/C, respectively) and in 8 healthy control
207 subjects. Systemic exposure (AUC) to lapatinib after a single oral 100-mg dose increased
208 approximately 14% and 63% in subjects with moderate and severe hepatic impairment,
209 respectively. Administration of TYKERB in patients with severe hepatic impairment should be
210 undertaken with caution due to increased exposure to the drug. A dose reduction should be
211 considered for patients with severe hepatic impairment [*see Dosage and Administration (2.2)*].

212 **10 OVERDOSAGE**

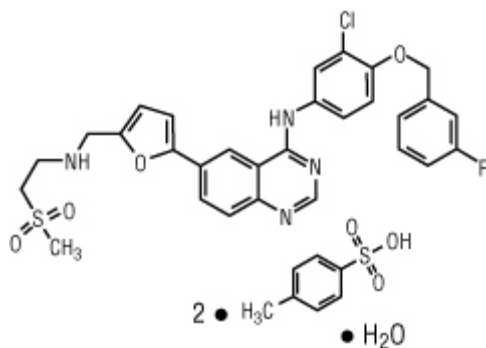
213 There is no known antidote for overdoses of TYKERB. The maximum oral doses of
214 lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent
215 ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical
216 trials and could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

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

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

224 **11 DESCRIPTION**

225 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase
226 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-
227 chloro-4-{{(3-fluorophenyl)methyl}oxy}phenyl)-6-[5-({[2-
228 (methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-
229 methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$
230 $(C_7H_8O_3S)_2 H_2O$ and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the
231 following chemical structure:



232
 233 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is
 234 0.001 mg/mL at 25°C.

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

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

241 12 CLINICAL PHARMACOLOGY

242 12.1 Mechanism of Action

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

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

254 12.3 Pharmacokinetics

255 **Absorption:** Absorption following oral administration of TYKERB is incomplete and
 256 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to
 257 1.5 hour). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours
 258 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to
 259 7 days, indicating an effective half-life of 24 hours.

260 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)
 261 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
 262 to 56 mcg.hr/mL).

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

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

269 Distribution: Lapatinib is highly bound (>99%) to albumin and alpha-1 acid
270 glycoprotein. In vitro studies indicate that lapatinib is a substrate for the transporters breast
271 cancer resistance protein (BCRP, ABCG2) and P-glycoprotein (Pgp, ABCB1). Lapatinib has also
272 been shown in vitro to inhibit these efflux transporters, as well as the hepatic uptake transporter
273 OATP 1B1, at clinically relevant concentrations.

274 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and
275 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated
276 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or
277 10% of lapatinib concentration in plasma.

278 Elimination: At clinical doses, the terminal phase half-life following a single dose was
279 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

280 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with
281 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of
282 27% (range 3 to 67%) of an oral dose.

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

285 **12.4 QT Prolongation**

286 The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-
287 label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses
288 of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and
289 Day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found
290 to have either QTcF (corrected QT by the Friedericia method) >480 msec or an increase in QTcF
291 >60 msec by automated machine-read evaluation of ECG. Analysis of the data suggested a
292 relationship between lapatinib concentration and the QTc interval.

293 **13 NONCLINICAL TOXICOLOGY**

294 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

295 Two-year carcinogenicity studies with lapatinib are ongoing.

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

301 There were no effects on male or female rat mating or fertility at doses up to
302 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times
303 the expected human clinical exposure based on AUC, respectively). The effect of lapatinib on
304 human fertility is unknown. However, when female rats were given oral doses of lapatinib during
305 breeding and through the first 6 days of gestation, a significant decrease in the number of live
306 fetuses was seen at 120 mg/kg/day and in the fetal body weights at ≥ 60 mg/kg/day
307 (approximately 6.4 times and 3.3 times the expected human clinical exposure based on AUC,
308 respectively).

309 **14 CLINICAL STUDIES**

310 The efficacy and safety of TYKERB in combination with capecitabine in breast cancer
311 were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2
312 (ErbB2) over-expressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic
313 breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and
314 trastuzumab.

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

326 Efficacy analyses four months after the interim analysis are presented in Table 3, Figure
327 1, and Figure 2.

328

329 **Table 3. Efficacy Results**

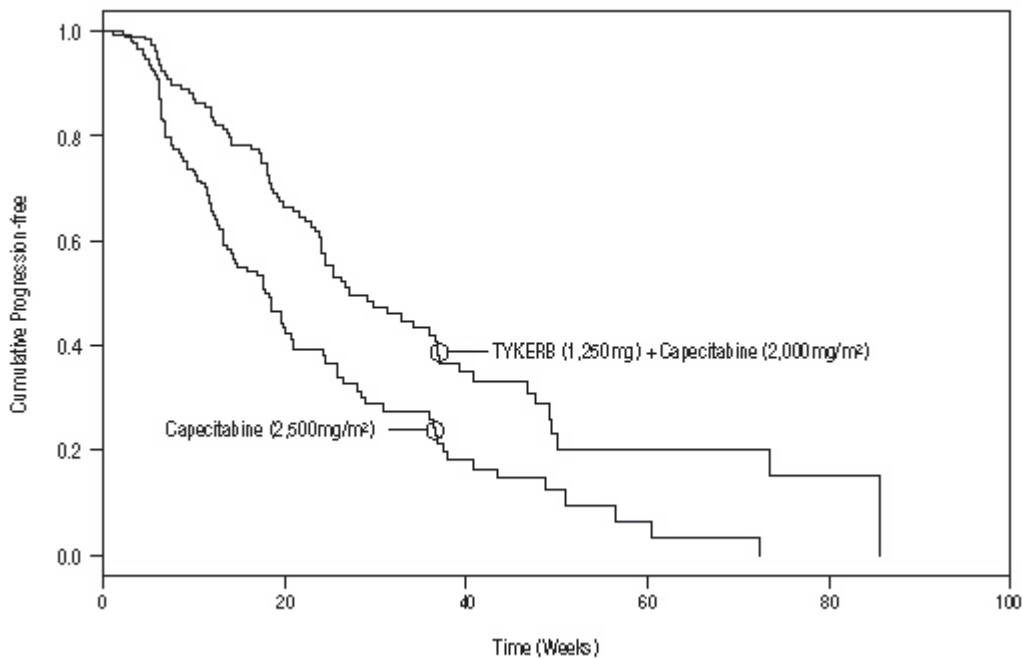
	Independent Assessment*		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
Number of TTP events	82	102	121	126
Median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

330 TTP = Time to progression.

331 * The time from last tumor assessment to the data cut-off date was >100 days in approximately
332 30% of patients in the independent assessment. The pre-specified assessment interval was 42 or
333 84 days.

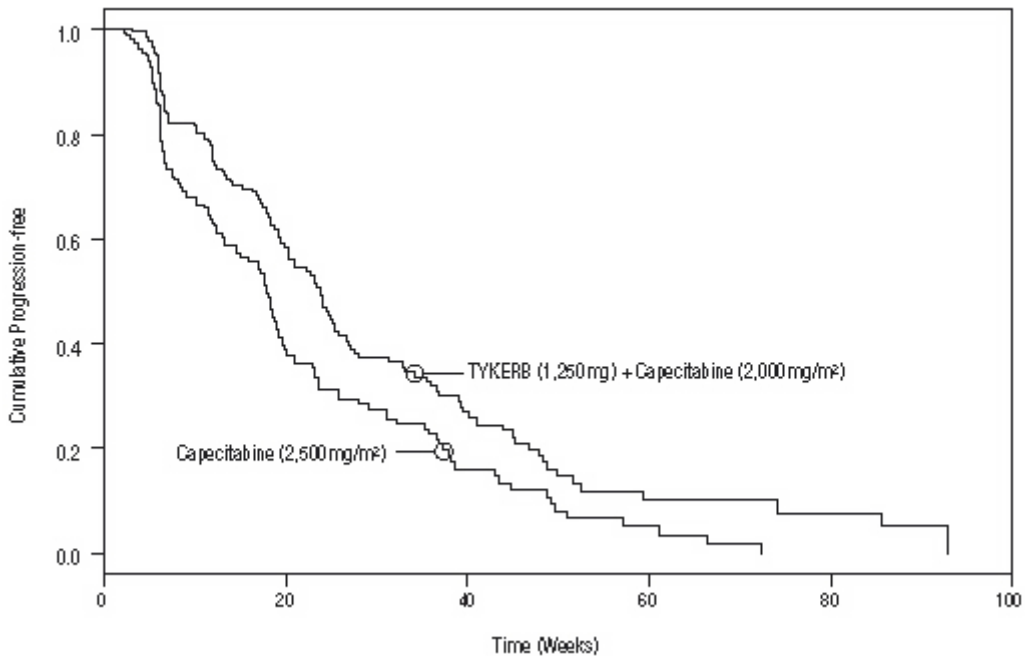
334

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



337

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



339
340 At the time of updated analysis, 30% of patients had died and the data for survival
341 analysis are not mature. Fifty-five patients (28%) in the TYKERB plus capecitabine group and
342 64 subjects (32%) in the capecitabine group had died.

343 **16 HOW SUPPLIED/STORAGE AND HANDLING**

344 The 250 mg tablets of TYKERB are oval, biconvex, orange, and film-coated with
345 GS XJG debossed on one side and are available in:
346 Bottles of 150 tablets: NDC 0173-0752-00
347 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP
348 Controlled Room Temperature].

349 **17 PATIENT COUNSELING INFORMATION**

350 *See FDA-approved patient labeling (17.6).*

351 **17.1 Decreased Left Ventricular Ejection Fraction**

352 Patients should be informed that TYKERB has been reported to decrease left ventricular
353 ejection fraction which may result in shortness of breath, palpitations, and/or fatigue. Patients
354 should inform their physician if they develop these symptoms while taking TYKERB.

355 **17.2 Diarrhea**

356 Patients should be informed that TYKERB often causes diarrhea which may be severe in
357 some cases. Patients should be told how to manage and/or prevent diarrhea and to inform their
358 physician if severe diarrhea occurs during treatment with TYKERB.

359 **17.3 Drug Interactions**

360 TYKERB may interact with many drugs; therefore, patients should be advised to report
361 to their healthcare provider the use of any other prescription or nonprescription medication or
362 herbal products.

363 **17.4 Food**

364 Patients should be informed of the importance of taking TYKERB at least one hour
365 before or one hour after a meal, in contrast to capecitabine which should be taken with food or
366 within 30 minutes after food.

367 **17.5 Divided Dosing**

368 The dose of TYKERB should not be divided. Patients should be advised of the
369 importance of taking TYKERB once daily, in contrast to capecitabine which is taken twice daily.

370 **17.6 FDA-Approved Patient Labeling**

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

373

374 TYKERB is a registered trademark of GlaxoSmithKline.

375



376

377 GlaxoSmithKline

378 Research Triangle Park, NC 27709

379

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384 **PATIENT INFORMATION**

385
386 **TYKERB[®] (TIE-curb)**
387 **(lapatinib) tablets**
388

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

392
393 **What is TYKERB?**

394 TYKERB is used with the medicine capecitabine for the treatment of patients with advanced or
395 metastatic breast cancer that is HER2 positive, and who have already had certain other breast
396 cancer treatments.

397
398 **Before you start taking TYKERB**, tell your doctor about all of your medical conditions,
399 including if you:

- 400 • have heart problems.
- 401 • have liver problems. You may need a lower dose of TYKERB.
- 402 • are pregnant or may become pregnant. TYKERB may harm an unborn baby. If you become
403 pregnant during treatment with TYKERB, tell your doctor as soon as possible.
- 404 • are breastfeeding. It is not known if TYKERB passes into your breast milk or if it can harm
405 your baby. If you are a woman who has or will have a baby, talk with your doctor about the
406 best way to feed your baby.

407
408 Tell your doctor about all the medicines you take, including prescription and nonprescription
409 medicines and herbal and dietary supplements. TYKERB and many other medicines may interact
410 with each other. Your doctor needs to know what medicines you take so he or she can choose the
411 right dose of TYKERB for you.

412
413 Especially tell your doctor if you take:

- 414 • antibiotics and anti-fungals (drugs used to treat infections)
- 415 • HIV (AIDS) treatments
- 416 • anticonvulsant drugs (drugs used to treat seizures)
- 417 • calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- 418 • antidepressants
- 419 • drugs used for stomach ulcers
- 420 • St. John's Wort or other herbal supplements

421

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

425

426 Because TYKERB is given with another drug called capecitabine, you should also discuss with
427 your doctor or pharmacist any medicines that should be avoided when taking capecitabine.

428

429 **How should I take TYKERB?**

- 430 • Take TYKERB exactly as your doctor has told you. TYKERB and capecitabine are taken in
431 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by mouth, **one time**
432 **a day on days 1 to 21**. Your doctor will tell you the dose of capecitabine you should take
433 and when you should take it.
- 434 • TYKERB should be taken at least one hour before, or at least one hour after food.
- 435 • Do not eat or drink grapefruit products while taking TYKERB.
- 436 • Your doctor may adjust your dose of TYKERB depending on how you tolerate the
437 treatment.
- 438 • If you forget to take your dose of TYKERB, take it as soon as you remember that day. If
439 you miss a day, do not double your dose the next day. Just skip the missed dose.

440

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

442 **Serious side effects** include:

- 443 • **heart problems**
 - 444 • decreased pumping of blood from the heart
 - 445 • abnormal heartbeat
- 446 • **lung problems**
- 447 • **severe diarrhea**, which may lead to you becoming dehydrated

448

449 **Call your doctor right away if you have palpitations, persistent cough, shortness of breath,**
450 **or severe diarrhea.**

451

452 **Common side effects** of TYKERB in combination with capecitabine include:

- 453 • diarrhea
- 454 • red, painful hands and feet
- 455 • nausea
- 456 • rash
- 457 • vomiting
- 458 • tiredness
- 459 • mouth sores
- 460 • loss of appetite

461 • indigestion

462

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

464

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

467

468 **You may also get side effects from capecitabine.** Talk to your doctor about possible side
469 effects with capecitabine.

470

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

472 • Store TYKERB tablets at room temperature between 59° and 86°F (15° to 30°C). Keep the
473 container closed tightly.

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

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

477

478 **General information about TYKERB**

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

483

484 This leaflet summarizes the most important information about TYKERB. If you would like more
485 information, talk with your doctor. You can ask your doctor or pharmacist for information about
486 TYKERB that is written for health professionals. For more information you can call toll-free 1-
487 888-825-5249.

488

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

490 **Active Ingredient:** Lapatinib.

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

494

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

496



497

498

499 Revised: Month YEAR

500 TKB:XPIL

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