

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TYKERB (lapatinib) tablets
Initial U.S. Approval: 2007

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

RECENT MAJOR CHANGES
Boxed Warning. Month YEAR
Hepatotoxicity. (5.2, 17.6) Month YEAR
Interstitial lung disease and pneumonitis. (5.5) August 2007

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)
• 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 prolongs the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.6)
• Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.7)

ADVERSE REACTIONS
The most common (>20%) adverse reactions during treatment with TYKERB plus capecitabine were diarrhea, palmar-plantar erythrodysesthesia, nausea, rash, vomiting, and fatigue. (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 **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 capecitabine for the treatment of patients with
8 advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received
9 prior therapy including an anthracycline, a taxane, and trastuzumab.

10 **2 DOSAGE AND ADMINISTRATION**

11 **2.1 Recommended Dosing**

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

20 **2.2 Dose Modification Guidelines**

21 **Cardiac Events:** TYKERB should be discontinued in patients with a decreased left
22 ventricular ejection fraction (LVEF) that is Grade 2 or greater by NCI Common Terminology
23 Criteria for Adverse Events (NCI CTCAE) and in patients with an LVEF that drops below the
24 institution's lower limit of normal [see *Warnings and Precautions (5.1) and Adverse Reactions*
25 *(6.1)*]. TYKERB may be restarted at a reduced dose (1,000 mg/day) after a minimum of 2 weeks
26 if the LVEF recovers to normal and the patient is asymptomatic.

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

32 **Concomitant Strong CYP3A4 Inhibitors:** The concomitant use of strong CYP3A4
33 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir,
34 indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit
35 may also increase plasma concentrations of lapatinib and should be avoided. If patients must be

36 coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction
37 to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without
38 inhibitors and should be considered. However, there are no clinical data with this dose
39 adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is
40 discontinued, a washout period of approximately 1 week should be allowed before the lapatinib
41 dose is adjusted upward to the indicated dose. [See *Drug Interactions (7.2)*.]

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

51 **Other Toxicities:** Discontinuation or interruption of dosing with TYKERB may be
52 considered when patients develop \geq Grade 2 NCI CTC toxicity and can be restarted at
53 1,250 mg/day when the toxicity improves to Grade 1 or less. If the toxicity recurs, then
54 TYKERB should be restarted at a lower dose (1,000 mg/day).

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

57 **3 DOSAGE FORMS AND STRENGTHS**

58 250 mg tablets — oval, biconvex, orange, film-coated with GS XJG debossed on one
59 side.

60 **4 CONTRAINDICATIONS**

61 None.

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

63 **5 WARNINGS AND PRECAUTIONS**

64 **5.1 Decreased Left Ventricular Ejection Fraction**

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

73 **5.2 Hepatotoxicity**

74 Hepatotoxicity (ALT or AST >3 times the upper limit of normal and total bilirubin
75 >1.5 times the upper limit of normal) has been observed in clinical trials (<1% of patients) and
76 postmarketing experience. The hepatotoxicity may be severe and deaths have been reported.
77 Causality of the deaths is uncertain. The hepatotoxicity may occur days to several months after
78 initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase)
79 should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as
80 clinically indicated. If changes in liver function are severe, therapy with TYKERB should be
81 discontinued and patients should not be retreated with TYKERB [*see Adverse Reactions (6.1)*].

82 **5.3 Patients with Severe Hepatic Impairment**

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

88 **5.4 Diarrhea**

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

93 **5.5 Interstitial Lung Disease/Pneumonitis**

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

99 **5.6 QT Prolongation**

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

109 **5.7 Pregnancy**

110 Pregnancy Category D

111 TYKERB can cause fetal harm when administered to a pregnant woman. In a study
112 where pregnant rats were dosed with lapatinib during organogenesis and through lactation, at a

113 dose of 120 mg/kg/day (approximately 6.4 times the human clinical exposure based on AUC),
114 91% of the pups had died by the fourth day after birth, while 34% of the 60 mg/kg/day pups were
115 dead. The highest no-effect dose for this study was 20 mg/kg/day (approximately equal to the
116 human clinical exposure based on AUC).

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

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

129 **6 ADVERSE REACTIONS**

130 **6.1 Clinical Trials Experience**

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

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

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

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

145

146 **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

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

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

150

151 **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

152 * National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
153

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

162 **Hepatotoxicity:** Lapatinib has been associated with hepatotoxicity [see Boxed Warning
163 and Warnings and Precautions (5.2)].

164 **Interstitial Lung Disease/Pneumonitis:** Lapatinib has been associated with interstitial
165 lung disease and pneumonitis in monotherapy or in combination with other chemotherapies [see
166 Warnings and Precautions (5.5)].

167 **7 DRUG INTERACTIONS**

168 **7.1 Effects of Lapatinib on Drug Metabolizing Enzymes and Drug Transport 169 Systems**

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

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

179 **7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes**

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

185 **Ketoconazole**: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at
186 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased to
187 approximately 3.6-fold of control and half-life increased to 1.7-fold of control.

188 **Carbamazepine**: In healthy subjects receiving the CYP3A4 inducer, carbamazepine, at
189 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure (AUC) to
190 lapatinib was decreased approximately 72%.

191 **7.3 Drugs that Inhibit Drug Transport Systems**

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

195 **7.4 Other Chemotherapy Agents**

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

198 **8 USE IN SPECIFIC POPULATIONS**

199 **8.1 Pregnancy**

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

201 **8.3 Nursing Mothers**

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

206 **8.4 Pediatric Use**

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

208 **8.5 Geriatric Use**

209 Of the total number of metastatic breast cancer patients in clinical studies of TYKERB in
210 combination with capecitabine (N = 198), 17% were 65 years of age and older, and 1% were
211 75 years of age and older. No overall differences in safety or effectiveness of the combination of
212 TYKERB and capecitabine were observed between these subjects and younger subjects, and
213 other reported clinical experience has not identified differences in responses between the elderly
214 and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

215 **8.6 Renal Impairment**

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

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

221 **8.7 Hepatic Impairment**

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

232 **10 OVERDOSAGE**

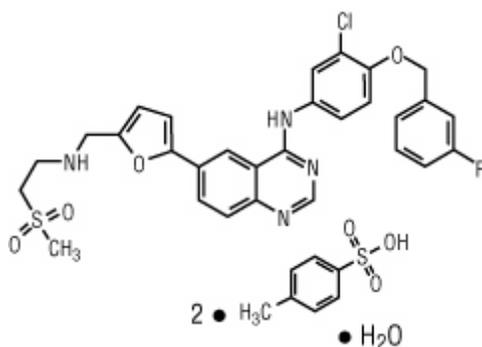
233 There is no known antidote for overdoses of TYKERB. The maximum oral doses of
234 lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent
235 ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical
236 trials and could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

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

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

244 **11 DESCRIPTION**

245 Lapatinib is a small molecule and a member of the 4-anilinoquinazoline class of kinase
246 inhibitors. It is present as the monohydrate of the ditosylate salt, with chemical name *N*-(3-
247 chloro-4-[[3-fluorophenyl)methyl]oxy]phenyl)-6-[5-({2-
248 (methylsulfonyl)ethyl}amino)methyl]-2-furanyl]-4-quinazolinamine bis(4-
249 methylbenzenesulfonate) monohydrate. It has the molecular formula $C_{29}H_{26}ClFN_4O_4S$
250 $(C_7H_8O_3S)_2 H_2O$ and a molecular weight of 943.5. Lapatinib ditosylate monohydrate has the
251 following chemical structure:



252
 253 Lapatinib is a yellow solid, and its solubility in water is 0.007 mg/mL and in 0.1N HCl is
 254 0.001 mg/mL at 25°C.

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

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

261 12 CLINICAL PHARMACOLOGY

262 12.1 Mechanism of Action

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

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

274 12.3 Pharmacokinetics

275 **Absorption:** Absorption following oral administration of TYKERB is incomplete and
 276 variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to
 277 1.5 hour). Peak plasma concentrations (C_{max}) of lapatinib are achieved approximately 4 hours
 278 after administration. Daily dosing of TYKERB results in achievement of steady state within 6 to
 279 7 days, indicating an effective half-life of 24 hours.

280 At the dose of 1,250 mg daily, steady state geometric mean (95% confidence interval)
 281 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
 282 to 56 mcg.hr/mL).

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

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

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

294 Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and
295 CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated
296 metabolites, none of which accounts for more than 14% of the dose recovered in the feces or
297 10% of lapatinib concentration in plasma.

298 Elimination: At clinical doses, the terminal phase half-life following a single dose was
299 14.2 hours; accumulation with repeated dosing indicates an effective half-life of 24 hours.

300 Elimination of lapatinib is predominantly through metabolism by CYP3A4/5 with
301 negligible (<2%) renal excretion. Recovery of parent lapatinib in feces accounts for a median of
302 27% (range 3 to 67%) of an oral dose.

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

305 **12.4 QT Prolongation**

306 The QT prolongation potential of lapatinib was assessed as part of an uncontrolled, open-
307 label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses
308 of lapatinib ranging from 175 mg/day to 1,800 mg/day. Serial ECGs were collected on Day 1 and
309 Day 14 to evaluate the effect of lapatinib on QT intervals. Thirteen of the 81 subjects were found
310 to have either QTcF (corrected QT by the Friedericia method) >480 msec or an increase in QTcF
311 >60 msec by automated machine-read evaluation of ECG. Analysis of the data suggested a
312 relationship between lapatinib concentration and the QTc interval.

313 **13 NONCLINICAL TOXICOLOGY**

314 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

315 Two-year carcinogenicity studies with lapatinib are ongoing.

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

321 There were no effects on male or female rat mating or fertility at doses up to
322 120 mg/kg/day in females and 180 mg/kg/day in males (approximately 6.4 times and 2.6 times
323 the expected human clinical exposure based on AUC, respectively). The effect of lapatinib on
324 human fertility is unknown. However, when female rats were given oral doses of lapatinib during
325 breeding and through the first 6 days of gestation, a significant decrease in the number of live
326 fetuses was seen at 120 mg/kg/day and in the fetal body weights at ≥ 60 mg/kg/day
327 (approximately 6.4 times and 3.3 times the expected human clinical exposure based on AUC,
328 respectively).

329 **14 CLINICAL STUDIES**

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

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

346 Efficacy analyses four months after the interim analysis are presented in Table 3, Figure
347 1, and Figure 2.

348

349 **Table 3. Efficacy Results**

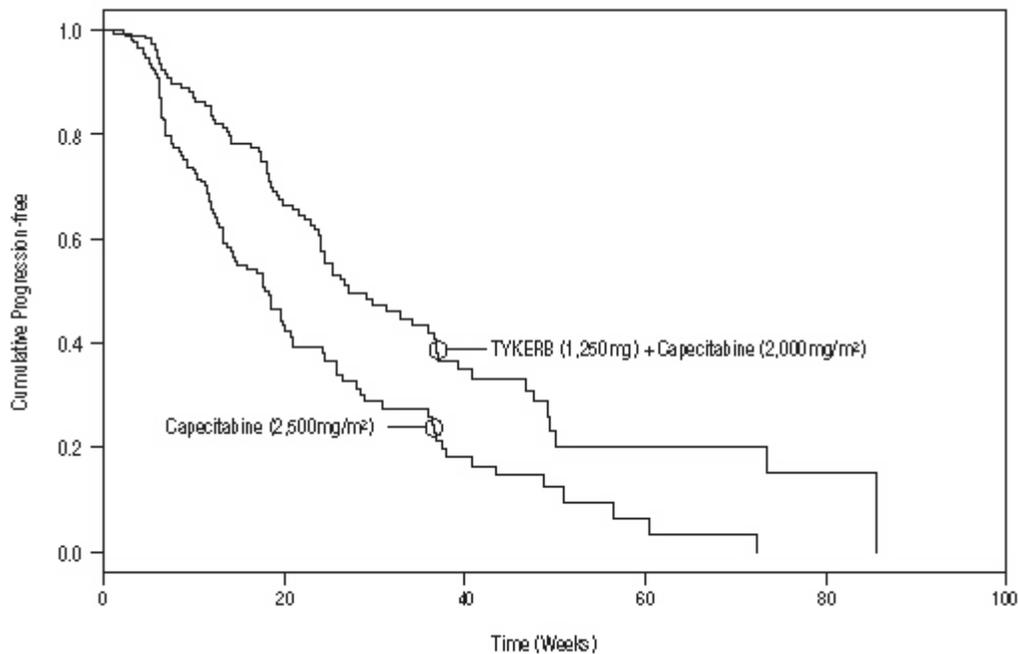
	Independent Assessment*		Investigator Assessment	
	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m ² /day	Capecitabine 2,500 mg/m ² /day
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
Number of TTP events	82	102	121	126
Median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

350 TTP = Time to progression.

351 * The time from last tumor assessment to the data cut-off date was >100 days in approximately
352 30% of patients in the independent assessment. The pre-specified assessment interval was 42 or
353 84 days.

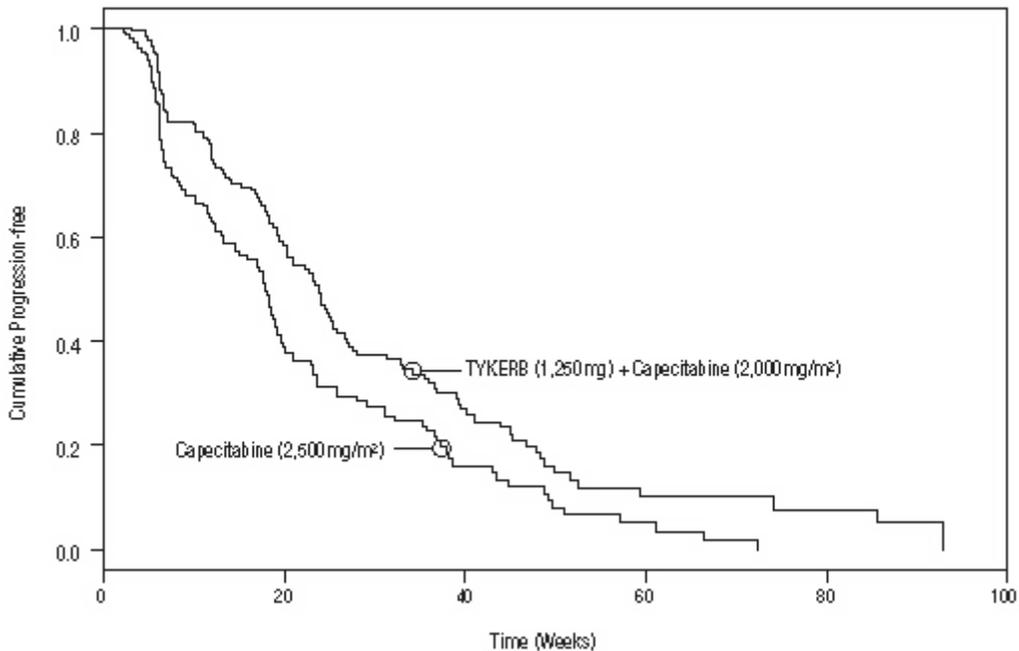
354

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



357

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



359
360 At the time of updated analysis, 30% of patients had died and the data for survival
361 analysis are not mature. Fifty-five patients (28%) in the TYKERB plus capecitabine group and
362 64 subjects (32%) in the capecitabine group had died.

363 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

369 **17 PATIENT COUNSELING INFORMATION**

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

371 **17.1 Decreased Left Ventricular Ejection Fraction**

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

375 **17.2 Diarrhea**

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

379 **17.3 Drug Interactions**

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

383 **17.4 Food**

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

387 **17.5 Divided Dosing**

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

390 **17.6 FDA-Approved Patient Labeling**

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

393

394 TYKERB is a registered trademark of GlaxoSmithKline.

395



396

397 GlaxoSmithKline

398 Research Triangle Park, NC 27709

399

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404 **PATIENT INFORMATION**

405
406 **TYKERB (TIE-curb)**
407 **(lapatinib) tablets**
408

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

412
413 **What is TYKERB?**

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

417
418 **Before you start taking TYKERB**, tell your doctor about all of your medical conditions,
419 including if you:

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

427
428 Tell your doctor about all the medicines you take, including prescription and nonprescription
429 medicines and herbal and dietary supplements. TYKERB and many other medicines may interact
430 with each other. Your doctor needs to know what medicines you take so he or she can choose the
431 right dose of TYKERB for you.

432
433 Especially tell your doctor if you take:

- 434 • antibiotics and anti-fungals (drugs used to treat infections)
- 435 • HIV (AIDS) treatments
- 436 • anticonvulsant drugs (drugs used to treat seizures)
- 437 • calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- 438 • antidepressants
- 439 • drugs used for stomach ulcers
- 440 • St. John's Wort or other herbal supplements

441

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

445

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

448

449 **How should I take TYKERB?**

- 450 • Take TYKERB exactly as your doctor has told you. TYKERB and capecitabine are taken in
451 21 day cycles. The usual dose of TYKERB is 1,250 mg (5 tablets) taken by mouth, **one time**
452 **a day on days 1 to 21**. Your doctor will tell you the dose of capecitabine you should take
453 and when you should take it.
- 454 • TYKERB should be taken at least one hour before, or at least one hour after food.
- 455 • Do not eat or drink grapefruit products while taking TYKERB.
- 456 • Your doctor may adjust your dose of TYKERB depending on how you tolerate the
457 treatment.
- 458 • If you forget to take your dose of TYKERB, take it as soon as you remember that day. If
459 you miss a day, do not double your dose the next day. Just skip the missed dose.

460

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

462 **Serious side effects** include:

- 463 • **heart problems**
 - 464 • decreased pumping of blood from the heart
 - 465 • abnormal heartbeat
- 466 • **liver problems**, which may cause itching, yellow eyes or skin, dark urine, or pain or
467 discomfort in the right upper area of the belly.
 - 468 • Your doctor should do blood tests to check your liver before you start taking TYKERB
469 and during treatment.
- 470 • **lung problems**
- 471 • **severe diarrhea**, which may lead to you becoming dehydrated

472

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

475

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

- 477 • diarrhea
- 478 • red, painful hands and feet
- 479 • nausea
- 480 • rash

- 481 • vomiting
- 482 • tiredness
- 483 • mouth sores
- 484 • loss of appetite
- 485 • indigestion

486

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

488

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

491

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

494

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

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

501

502 **General information about TYKERB**

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

507

508 This leaflet summarizes the most important information about TYKERB. If you would like more
509 information, talk with your doctor. You can ask your doctor or pharmacist for information about
510 TYKERB that is written for health professionals. For more information you can call toll-free 1-
511 888-825-5249.

512

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

514 **Active Ingredient:** Lapatinib.

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

518

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

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TYKERB is a registered trademark of GlaxoSmithKline.



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Research Triangle Park, NC 27709

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Revised: Month YEAR

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