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

----------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/m^2/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 prolongs the QT interval in some patients. Consider ECG and electrolyte monitoring. (5.4)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking TYKERB. (5.5)

---------- 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: March 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TYKERB 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

2.2 Dose Modification Guidelines

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

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

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

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

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

Other Toxicities: Discontinuation or interruption of dosing with TYKERB may be considered when patients develop greater than or equal to grade 2 NCI CTC toxicity and can be restarted at 1,250 mg/day when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (1,000 mg/day).

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

See manufacturer's prescribing information for capecitabine contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Left Ventricular Ejection Fraction

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

5.2 Patients with Severe Hepatic Impairment

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

5.3 Diarrhea

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

5.4 QT prolongation

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

5.5 Pregnancy

Pregnancy Category D

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

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of TYKERB has been evaluated in more than 3,500 patients in clinical trials. The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was

evaluated in 198 patients in a randomized, Phase 3 trial. *[See Clinical Studies (14).]* Adverse reactions which occurred in at least 10% of patients in either treatment arm and were higher in the combination arm are shown in Table 1.

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

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

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

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

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

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

Table 2. Selected Laboratory Abnormalities

Parameters	TYKERB 1,250 mg/m^2/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 patients 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).]*

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.

7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations significantly *(see Ketoconazole and Carbamazepine sections, below)*. Dose adjustment of lapatinib should be

considered for patients who must receive concomitant strong inhibitors or concomitant strong inducers of CYP3A4 enzymes *[see Dosage and Administration (2.2)]*.

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

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

7.3 Drugs that Inhibit Drug Transport Systems

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

7.4 Other Chemotherapy Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.5)].

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

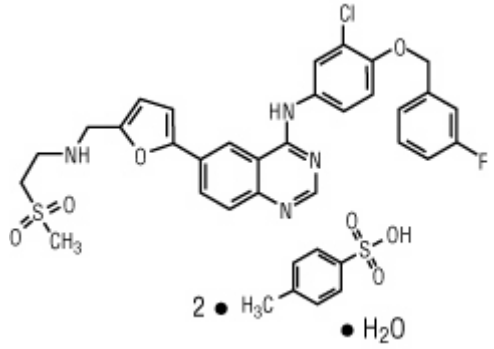
There is no known antidote for overdoses of TYKERB. The maximum oral doses of lapatinib that have been administered in clinical trials are 1,800 mg once daily. More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials and could result in increased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

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

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

11 DESCRIPTION

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



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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

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

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

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

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

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

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

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

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

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

12.4 QT Prolongation

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies with lapatinib are ongoing.

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

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

14 CLINICAL STUDIES

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer were evaluated in a randomized, Phase 3 trial. Patients eligible for enrollment had HER2 (ErbB2) over-expressing (IHC 3+ or IHC 2+ confirmed by FISH), locally advanced or metastatic

breast cancer, progressing after prior treatment that included anthracyclines, taxanes, and trastuzumab.

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

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

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 (25th, 75th, 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)

TTP = Time to progression.

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

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

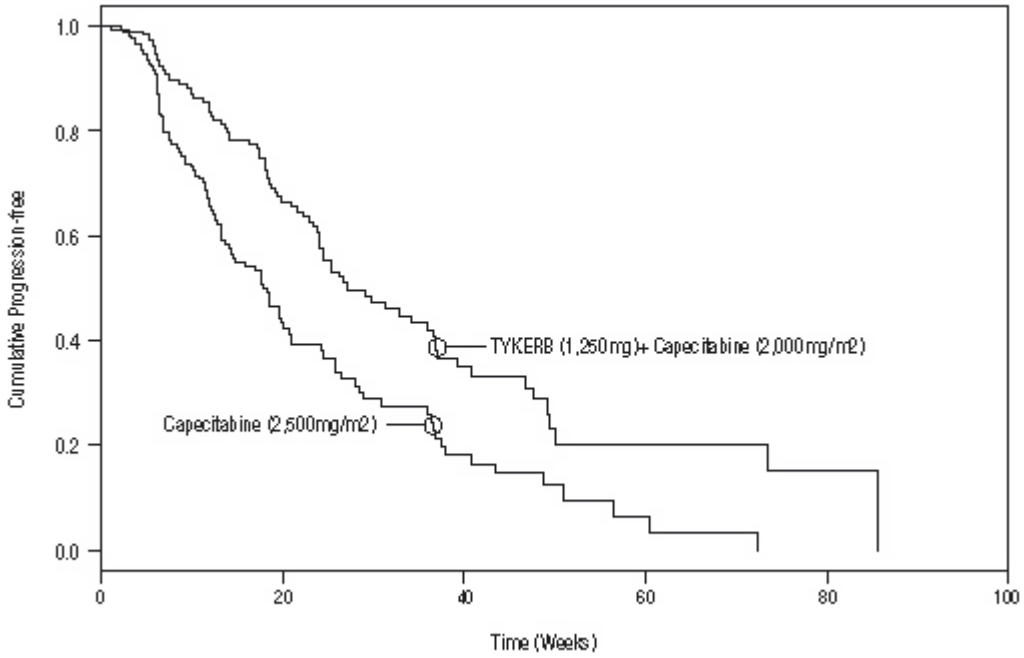
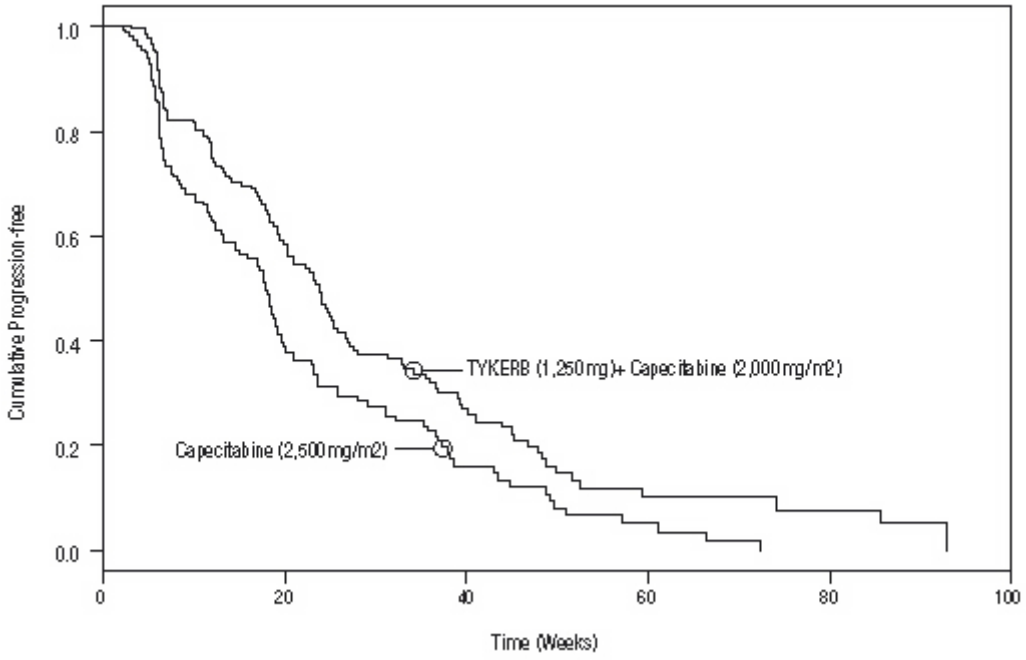


Figure 2. Kaplan-Meier Estimates for Investigator Assessment Time to Progression



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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Bottles of 150 tablets: NDC 0173-0752-00

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (17.6)

17.1 Decreased Left Ventricular Ejection Fraction

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

17.2 Diarrhea

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

17.3 Drug Interactions

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

17.4 Food

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

17.5 Divided Dosing

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

17.6 FDA Approved Patient Labeling

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

17.6 FDA-Approved Patient Labeling

PATIENT INFORMATION

TYKERB® (TIE-curb) (lapatinib) tablets

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

What is TYKERB?

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

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

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

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

Especially tell your doctor if you take:

- antibiotics and anti-fungals (drugs used to treat infections)
- HIV (AIDS) treatments
- anticonvulsant drugs (drugs used to treat seizures)
- calcium channel blockers (drugs used to treat certain heart disorders or high blood pressure)
- antidepressants
- drugs used for stomach ulcers

- St. John’s Wort or other herbal supplements

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

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

How should I take TYKERB?

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

What are the possible side effects of TYKERB?

Serious side effects include:

- **heart problems**
  - decreased pumping of blood from the heart
  - abnormal heart beat

  Call your doctor right away if you have palpitations or are short of breath.
- **severe diarrhea**, which may lead to you becoming dehydrated

Common side effects of TYKERB in combination with capecitabine include:

- diarrhea
- red, painful hands and feet
- nausea
- rash
- vomiting
- tiredness
- mouth sores
- loss of appetite
- indigestion

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

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

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

How should I store TYKERB tablets?

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

General information about TYKERB

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

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

What are the ingredients in TYKERB?

Active Ingredient: Lapatinib.

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

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

TYKERB is a trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

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