PRODUCT MONOGRAPH

PrTYKERB®

lapatinib tablets
(as lapatinib ditosylate)

250 mg

Antineoplastic

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PrTYKERB®

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/250 mg lapatinib as lapatinib ditosylate	Hypromellose, iron oxide red, iron oxide yellow, macrogol/PEG 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

INDICATIONS AND CLINICAL USE

TYKERB (lapatinib ditosylate) is indicated in combination with capecitabine for the treatment of patients with metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressed on taxanes and anthracycline before starting this therapy. In addition, patients should have progressed on prior trastuzumab therapy in the metastatic setting.

Approval is based on the surrogate endpoint, time to progression, without demonstration of an overall survival advantage or palliation due to therapy (see PART II, CLINICAL TRIALS).

TYKERB is indicated in combination with letrozole for the treatment of post-menopausal patients with hormone receptor positive metastatic breast cancer, whose tumours overexpress the ErbB2 (HER2) receptor, and who are suitable for endocrine therapy. Approval was based on progression free survival, without demonstrating an overall survival advantage or quality of life benefit.

CONTRAINDICATIONS

TYKERB is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

Please refer to the product monograph of the co-administered medicinal products (capecitabine or letrozole) for relevant contraindications and safety information.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TYKERB (lapatinib ditosylate) should only be administered by physicians experienced with antineoplastic drugs (see INDICATIONS and CLINICAL USE).

- Hepatotoxicity, may be severe and deaths have been reported (see Hepatic/Biliary/Pancreatic section below)
- Decreases in left ventricular ejection fraction (LVEF) (see Cardiovascular section below)
- QT/QTc prolongation (see Cardiovascular section below)
- Diarrhea may be severe, and deaths have been reported (see Gastrointestinal section below)

General

It is not recommended that lapatinib in combination with letrozole be administered to HER2 negative patients due to a lack of clinical benefit in this population (see CLINICAL TRIALS).

Cardiovascular

LVEF and Heart Failure: TYKERB has been reported to decrease left ventricular ejection fraction [LVEF] (see ADVERSE REACTIONS). In randomized clinical trials, the majority (>57%) of LVEF decreases occurred within the first 12 weeks of treatment, but data on long-term exposure are limited. 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 institutions normal limits. LVEF should continue to be evaluated during treatment with TYKERB to ensure that LVEF does not decline to an unacceptable level. Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Cardiac Events and PART II, CLINICAL TRIALS).

QT/QTc Prolongation: TYKERB is associated with QT/QTc interval prolongation (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY). Many drugs that cause QT/QTc prolongation are suspected to increase the risk of torsade de pointes. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Events of ventricular fibrillation, cardiac arrest, and sudden death have been reported with TYKERB in clinical trials.

QT prolongation was observed in an uncontrolled, open-label dose escalation study of lapatinib in advanced cancer patients. A concentration dependent increase of the QTc interval has also been confirmed in a dedicated placebo-controlled crossover study in subjects with advanced solid tumors (see section ACTION AND CLINICAL PHARMACOLOGY).

Caution should be taken if TYKERB is administered to patients who have or may develop prolongation of QTc. These conditions include patients with hypokalemia or hypomagnesemia, congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. Hypokalemia, hypocalcaemia or hypomagnesemia should be corrected prior to lapatinib administration.

Particular care should be exercised when administering TYKERB to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QT/QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia); bradycardia (<50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); nutritional deficits (e.g., eating disorders, extreme diets); diabetes mellitus; autonomic neuropathy; hepatic dysfunction.

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Drug Interactions

Concomitant treatment with inhibitors or inducers of CYP3A4, including grapefruit juice, should be avoided due to risk of increased or decreased exposure to TYKERB, respectively (see DRUG INTERACTIONS).

Concomitant treatment with other QT-prolonging drugs should be avoided to the extent possible (see DRUG INTERACTIONS).

Gastrointestinal

Diarrhea, including severe diarrhea, has been reported with TYKERB treatment (see ADVERSE REACTIONS). Diarrhea may be severe, and deaths have been reported.

Diarrhea generally occurs early during TYKERB treatment, with almost half of those patients with diarrhea first experiencing it within 6 days. This usually lasts 4-5 days. TYKERB -induced diarrhea is usually low-grade, with severe diarrhea of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grades 3 and 4 occurring in <10% and <1% of patients, respectively. Early identification and intervention is critical for the optimal management of diarrhea. At the start of therapy, the patient's bowel pattern and other symptoms (e.g. fever, cramping pain, nausea, vomiting, dizziness and thirst) should be determined, to allow identification of changes during treatment and to help identify patients at greater risk of diarrhea. Patients should be instructed to promptly report any change in bowel patterns immediately. Proactive management of diarrhea with anti-diarrhea agents is important. Prompt treatment after the first unformed stool is recommended with reassessment at 24 hours advised. Severe cases of diarrhea (CTCAE grade 3 or 4, grades 1 or 2 with complicating features such as severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration) may require administration of oral or intravenous electrolytes and fluids as indicated, use of antibiotics such as fluoroquinolones and interruption or discontinuation of TYKERB therapy (see DOSAGE AND ADMINISTRATION, Dosing Considerations, Diarrhea). Please refer to the capecitabine product monograph for relevant safety information.

Hepatic/Biliary/Pancreatic

Hepatotoxicity (ALT or AST > 3 times the upper limit of normal and total bilirubin > 1.5 times the upper limit of normal) has been observed in clinical trials (< 1% of patients) and post-marketing experience (see ADVERSE REACTIONS). The hepatotoxicity may be severe and deaths have been reported. The hepatotoxicity may occur days to several months after initiation of treatment. Liver function tests (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment, and as clinically indicated. If changes in liver function are severe, therapy with TYKERB should be discontinued and patients should not be retreated with lapatinib. Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of TYKERB -associated hepatotoxicity. In a large, randomised clinical trial of TYKERB monotherapy (n=1,194), the overall risk of severe liver injury (ALT >5 times the upper limit of normal, NCI CTCAE grade 3) was 2% (1:50), the risk in DQA1*02:01 and DRB1*07:01 allele carriers was 8% (1:12) and the risk in non-carriers was 0.5% (1:200). Carriage of the HLA risk alleles is common (15 to 25%) in Caucasian, Asian, African and Hispanic populations but lower (1%) in Japanese populations.

There is no clinical experience with TYKERB in patients with severe pre-existing hepatic impairment. If TYKERB is to be administered to patients with severe pre-existing hepatic impairment, a dose reduction is recommended based on pharmacokinetic modeling. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with TYKERB (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Hepatic Impairment).

Respiratory

TYKERB has been associated with reports of interstitial lung disease and pneumonitis (see ADVERSE REACTIONS). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis. TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are ≥ Grade 3 (see DOSAGE AND ADMINISTRATION).

Skin

Severe cutaneous reactions have been reported with TYKERB. If erythema multiforme or life-threatening reactions such as Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g. progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with TYKERB (see DOSAGE AND ADMINISTRATION).

As dermatologic adverse reactions such as rash and palmar-plantar dysesthesia were very commonly reported in clinical trials (see ADVERSE REACTIONS), physicians are advised to perform a skin examination prior to treatment and regularly during treatment. Lapatinib may increase the risk of photosensitivity. Patients should be encouraged to avoid exposure to sunlight and apply broad spectrum sunscreens with an SPF ≥30. If a skin reaction occurs a full body examination should be performed at every visit until one month after resolution. Patients with extensive or persistent skin reactions should be referred to a dermatologist.

Special Populations

Pregnant Women: TYKERB can cause fetal harm when administered to a pregnant woman (See PART II, TOXICOLOGY). There are no adequate and well-controlled studies of TYKERB in pregnant women. Women of childbearing potential should be advised to use adequate contraception and avoid becoming pregnant while receiving TYKERB and for at least 5 days after the last dose. 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.

TYKERB was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic (see PART II, TOXICOLOGY).

Nursing Women: It is not known whether TYKERB is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfeeding infants from TYKERB, it is recommended that women should not breast-feed while receiving TYKERB and for at least 5 days after the last dose.

Pediatrics: The safety and efficacy of TYKERB in pediatric patients have not been established.

Geriatrics (> 65 years of age): There are limited data of the use of TYKERB in patients aged 65 years and older. Of the total number of metastatic breast cancer patients in

clinical studies of TYKERB in combination with capecitabine (N=198) 17% were 65 and over and 1% were 75 and over. No overall differences in safety were observed between these subjects and younger subjects. Of the total number of hormone sensitive metastatic breast cancer patients in the clinical studies of lapatinib in combination with letrozole (N=642) 44% were 65 and over and 12% were 75 and over. No overall differences in safety of the combination of lapatinib and letrozole were observed between these subjects and younger subjects. However, peripheral edema was not commonly reported by subjects in the <65 years of age group. 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. In the clinical study of lapatinib in combination with letrozole, the median time to onset of a cardiac event was shorter for subjects aged 65 and over in the letrozole plus lapatinib group (16.43 weeks) compared with the letrozole plus placebo group (44.14 weeks) (in the 'all patients' population).

Monitoring and Laboratory Tests

Hypokalemia, hypomagnesemia, or hypocalcemia should be corrected prior to administration of TYKERB. The prescriber should consider baseline and on-treatment electrolyte measurements and electrocardiograms with QT measurement.

Prior to the initiation of treatment, left ventricular ejection fraction (LVEF) must be evaluated to ensure that baseline LVEF is within the institutional limits of normal (see WARNINGS AND PRECAUTIONS). LVEF must continue to be monitored during treatment with TYKERB to ensure that LVEF does not decline below the institutional lower limit of normal. LVEF was monitored at approximately 8 week intervals during treatment with TYKERB in clinical trials (see Recommended Dose and Dosing Adjustments).

Liver function (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment, every 4 to 6 weeks during treatment and as clinically indicated. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.

Physicians are advised to perform a skin examination prior to treatment and regularly during treatment.

Ability to perform tasks that require judgement, motor or cognitive skills

There have been no studies to investigate the effect of TYKERB on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of lapatinib. The clinical status of the patient and the adverse event profile of TYKERB should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

TYKERB has been evaluated for safety as a single agent and in combination with other chemotherapies in more than 12,000 patients with various cancers.

TYKERB/capecitabine Combination

The safety of TYKERB in combination with capecitabine in advanced and metastatic breast cancer was evaluated in 198 patients in a randomized, phase III trial (See CLINICAL TRIALS). Adverse events (regardless of causality) which occurred in at least 5% of patients in either treatment arm are shown in Table 1.

Table 1 Adverse Events from Clinical Trial EGF100151 (Without Regard to Causality) Occurring in ≥5% of Patients

	TYKERB + Capecitabine (N = 198)			Capecitabine (N = 191)		
Event	**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
Abdominal pain	13	1	0	16	1	0
Stomatitis	14	0	0	11	<1	0
Constipation	10	0	0	12	1	0
Abdominal pain upper	9	0	0	6	0	0
Dyspepsia	11	<1	0	3	0	0
General disorders and administrative site conditions						
Fatigue	23	3	0	25	3	<1
Mucosal inflammation	15	0	0	12	2	0
Asthenia	10	1	<1	13	2	0
Pyrexia	8	0	0	6	0	0
Oedema peripheral	6	<1	0	4	<1	0
Infections and infestations						
Nasopharyngitis	4	0	0	7	0	0
Metabolism and Nutrition Disorders						
Anorexia	14	<1	0	19	<1	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Arthralgia	7	<1	0	4	0	0
Bone Pain	7	<1	0	4	<1	0
Nervous system disorder						
Headache	10	0	0	14	<1	<1
Dizziness	4	0	0	8	<1	<1
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Cough	7	0	0	8	0	0
Epistaxis	8	0	0	2	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0

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

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

None of the listed Adverse Events met the criteria for Grade 5.

The most common adverse reactions during therapy with TYKERB plus capecitabine were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysaesthesia and rash), and fatigue. Diarrhea was the most common adverse reaction (60% all grades) resulting in discontinuation of study medication (5% of patients). The most common Grade 3 and 4 adverse reactions (NCI CTC v3) were diarrhea and palmar-plantar erythrodysaesthesia.

Selected laboratory abnormalities are shown in Table 2. The majority of adverse events and laboratory abnormalities were Grades 1 or 2.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 Selected Laboratory Abnormalities

	TYKERB + Capecitabine			Capecitabine		
Event	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Hematologic						
Hemoglobin	56	<1	0	53	1	0
Neutrophils	22	3	<1	31	2	1
Platelets	18	<1	0	17	<1	<1
Hepatic						
AST	49	2	<1	43	2	0
Total Bilirubin**	45	4	0	30	3	0
ALT	37	2	0	33	1	0

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

** Elevated bilirubin may be due to lapatinib inhibition of hepatic uptake by OATP1B1, Pgp or BCRP (see DRUG INTERACTIONS section).

TYKERB/letrozole Combination

The increase in lapatinib dose from 1250 mg to 1500 mg was evaluated in combination with letrozole in a Phase I study. The study demonstrated a similar adverse event profile for each dose, however, very few individuals were included in the 1250 mg arm making a comparison difficult.

In a randomized clinical trial of patients (N=1286) with hormone receptor positive advanced or metastatic breast cancer, who had not received chemotherapy for their metastatic disease, patients received letrozole with or without TYKERB. In this trial, the safety profile of TYKERB was consistent with previously reported results from trials of TYKERB in the advanced or metastatic breast cancer population. 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 3. Selected laboratory abnormalities are shown in Table 4.

Table 3 Adverse Events from Clinical Trial EGF30008 (Without Regard To Causality) Occurring in ≥ 10% Patients

System organ class MedDRA preferred term	Number (%) of subjects					
	TYKERB 1500 mg + Letrozole 2.5 mg (N=654)			Letrozole 2.5 mg + Placebo (N=624)		
	All Grades[a] %	Grade 3 %	Grade 4 %	All Grades[a] %	Grade 3 %	Grade 4 %
Metabolism and nutrition disorders						
Anorexia	11	<1	0	9	<1	0
Nervous system disorders						
Headache	14	<1	0	13	<1	0
Gastrointestinal disorders						
Diarrhea	64	9	<1	20	<1	0
Nausea	31	<1	0	21	<1	0
Vomiting	17	1	<1	11	<1	<1
Skin and subcutaneous tissue disorders						
Rash[b]	44	1	0	13	0	0
Pruritus	12	<1	0	9	<1	0
Alopecia	13	<1	0	7	0	0
Dry skin	13	<1	0	4	0	0
Nail disorder	11	<1	0	<1	0	0
General disorders and administrative site conditions						
Fatigue	20	2	0	17	<1	0
Asthenia	12	<1	0	11	<1	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	11	<1	0	2	<1	0

a. National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.
b. In addition to the rash reported under "Skin and subcutaneous tissue disorders", 3 additional subjects in each treatment group had a rash reported under "Infections and infestations"; none were Grade 3 or 4.
Grade 3=severe AE; Grade 4=life threatening or disabling AE.

Table 4 Selected Laboratory Abnormalities

	TYKERB 1500 mg/day + Letrozole 2.5 mg/day			Letrozole 2.5 mg/day + Placebo		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Hepatic Parameters	%	%	%	%	%	%
Total Bilirubin	22	<1	<1	11	1	<1
AST	53	6	0	36	2	<1
ALT	46	5	<1	35	1	0

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

Rash occurred in approximately 28% of patients who received TYKERB in combination with capecitabine and in 44% of patients who received TYKERB in combination with letrozole. Rash was generally low grade and did not result in discontinuation of treatment with TYKERB.

Other Clinical Trial Adverse Drug Reactions

Cardiotoxicity
Rare but serious events of congestive heart failure, cardiac arrest and sudden death have been reported with TYKERB. Due to potential cardiac toxicity with ErbB2 (HER2) inhibitors, LVEF was monitored in clinical trials at approximately 8-week intervals. Decreases in LVEF were considered a Serious Adverse Event (SAE) if signs or symptoms of deterioration in LVEF were ≥ Grade 3 (NCI CTCAE), or in cases of a ≥ 20% decrease in LVEF relative to baseline value and below the institution's lower limit of normal. In study EGF100151, among 177 patients who received lapatinib plus capecitabine and had screening, plus at least one on-treatment LVEF measurement, 10 patients (6%) experienced a ≥ 20% decrease in LVEF, including 4 patients (2%) that met the SAE criteria above. Amongst 150 patients who received capecitabine monotherapy and had screening, plus at least one on treatment LVEF measurement, 9 patients (6%) experienced a ≥ 20% decrease in LVEF, including 4 patients (3%) that met the SAE criteria.

In 3 supportive monotherapy studies, among 338 patients who had screening, plus at least one on treatment LVEF measurement, 17 patients (5%) experienced a ≥ 20% decrease in LVEF, including 7 patients (2.1%) that met the SAE criteria (see WARNINGS and PRECAUTIONS, Cardiotoxicity).

In study EGF30008, 3.1% and 1.3% of patients met the SAE criteria above, in the TYKERB plus letrozole and letrozole alone treatment arms, respectively.

Hepatotoxicity
TYKERB has been associated with hepatotoxicity. In clinical trials, it has been observed in <1% of patients, but may be severe and deaths have been reported. See WARNINGS and PRECAUTIONS, Hepatotoxicity section.

Respiratory, Thoracic and Mediastinal Disorders
TYKERB has been associated with interstitial lung disease and pneumonitis in monotherapy or in combination with other chemotherapies. See WARNINGS and PRECAUTIONS, Respiratory section.

Immune System Disorders
TYKERB has been associated with hypersensitivity reactions including anaphylaxis. See CONTRAINDICATIONS section.

Skin and Subcutaneous Tissue Disorders
Nail disorders including paronychia have been reported.

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been derived from post-marketing experience with TYKERB via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Cardiac disorders
Ventricular arrhythmias/Torsades de Pointes (TdP)
Electrocardiogram QT prolonged
Skin and subcutaneous tissue disorders
Severe cutaneous adverse reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

DRUG INTERACTIONS

Drug-Drug Interactions
Lapatinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter lapatinib concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics and WARNINGS AND PRECAUTIONS).

In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure (AUC) to lapatinib was increased approximately 3.6 fold of control and half-life increase to 1.7 fold of control. The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanivir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit may also increase plasma concentrations of lapatinib and should be avoided. If patients must be co-administered a strong CYP3A4 inhibitor, a dose reduction should be considered. (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). Co-administration of lapatinib with moderate inhibitors of CYP3A4 should proceed with caution and clinical adverse reactions should be carefully monitored.

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 by approximately 72%. 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 co-administered a strong CYP3A4 inducer, the dose of lapatinib should be adjusted (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Pre-treatment with a proton pump inhibitor (esomeprazole) decreased lapatinib exposure by an average of 27% (range: 6% to 49%). This effect decreases with increasing age from approximately 40 to 60 years. Therefore, caution should be used when lapatinib is used in patients pre-treated with a proton pump inhibitor.

The concomitant use of TYKERB with another QT/QTc-prolonging drug should be avoided to the extent possible. Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide), Class 1C antiarrhythmics (e.g., flecainide, propafenone), anthracyclines, including a history of prior treatment (e.g., doxorubicin, epirubicin), tyrosine kinase inhibitors (e.g., sunitinib), antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone), antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline), opioids (e.g., methadone), macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin), quinolone antibiotics (e.g., moxifloxacin, levofloxacin), pentamidine, antimalarials (e.g., quinine, chloroquine), azole antifungals (e.g., ketoconazole, fluconazole, voriconazole), domperidone, 5-HT_3 receptor antagonists (e.g., dolasetron, ondansetron), tacrolimus, beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

As plasma levels of lapatinib can be increased by inhibitors of CYP3A4, prolongation of the QT/QTc interval by TYKERB is anticipated to be increased in the presence of CYP3A4 inhibitors. The concomitant use of these drugs with TYKERB is discouraged.

The use of TYKERB is discouraged with drugs that can disrupt electrolyte levels, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

TYKERB inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Coadministration of lapatinib with orally administered midazolam resulted in an approximate 45% increase in the AUC of midazolam. There was no clinically meaningful increase in AUC when midazolam was dosed intravenously. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered

when dosing TYKERB concurrently with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). TYKERB is anticipated to decrease the metabolism/increase the bioavailability of the following CYP3A4 substrates that also prolong the QT/QTc interval: clarithromycin, erythromycin, telithromycin, quinidine, quinine, ondansetron, haloperidol, pimozide, ziprasidone, salmeterol, methadone, and domperidone. The concomitant use of these drugs with TYKERB is discouraged.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval, inhibit CYP3A4, or cause electrolyte disturbances, as well as for older drugs for which these effects have recently been established.

Lapatinib inhibits CYP2C8 *in vitro* at clinically relevant concentrations. Caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Lapatinib is a substrate for the transport proteins P-glycoprotein and BCRP (Breast Cancer Resistance Protein). Inhibitors (e.g. quinidine and cyclosporine A) and inducers (e.g. rifampicin and dexamethasone) of these proteins may alter the exposure and/or distribution of lapatinib, and caution should be exercised (see Pharmacokinetics). The QT/QTc prolongation caused by TYKERB is expected to be increased in the presence of inhibitors of these transport proteins.

Lapatinib inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations. Coadministration of lapatinib with orally administered digoxin, also a substrate for Pgp, resulted in an approximate 98% increase in the AUC of digoxin. Due to its narrow therapeutic window, monitoring of serum digoxin concentrations should be performed at the beginning of coadministration with lapatinib. Caution should be exercised when dosing lapatinib concurrently with digoxin or other medications with narrow therapeutic windows that are substrates of Pgp.

TYKERB inhibits the transport proteins BCRP and OATP1B1 *in vitro*. The clinical relevance of this effect has not been evaluated, although it may cause elevated bilirubin due to lapatinib inhibition of hepatic uptake by OATP1B1 or inhibition of excretion into bile by Pgp or BCRP. If TYKERB is administered with drugs that are substrates of BCRP or OATP1B1 (e.g. rosuvastatin), increased concentrations of the substrate drug are likely, and caution should be exercised (see Pharmacokinetics).

Concomitant administration of TYKERB with capecitabine or letrozole did not meaningfully alter the pharmacokinetics of either agent (or the metabolites of capecitabine), or TYKERB.

Drug-Food Interactions

The bioavailability of TYKERB is increased by food. TYKERB should only be taken at least 1 hour before or at least 1 hour after a low-fat meal (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Grapefruit juice may inhibit CYP3A4 in the gut wall and increase the bioavailability of lapatinib and should therefore be avoided during treatment with lapatinib.

DOSAGE AND ADMINISTRATION

TYKERB should only be administered by physicians experienced with antineoplastic drugs (see INDICATIONS AND CLINICAL USE).

ErbB2 (HER2) over-expressing tumours are defined by IHC3+, IHC2+ and gene amplification (FISH), or gene amplification alone. Gene amplification should be performed using an accurate and validated assay. Tumour tissue is ErbB2 (HER2) positive by FISH if the ratio is greater than 2.0 and by IHC with IHC3+ and full circumferential staining in >10% tumour cells.

Dosing Considerations

The bioavailability of lapatinib is increased by food. TYKERB should only be taken at least 1 hour before or at least 1 hour after a low-fat meal. The recommended daily lapatinib dose should not be divided.

Recommended Dose and Dosage Adjustment

TYKERB/capecitabine Combination
The recommended dose of TYKERB is 1250 mg (i.e. five tablets) once daily every day when taken in combination with capecitabine. TYKERB should be taken at least one hour before, or at least one hour after a low fat meal (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The recommended dose of capecitabine is 2000 mg/m^2/day divided into two equal doses, each dose taken 12 hours apart on days 1-14 in a 21 day cycle (see PART II, CLINICAL TRIALS). Capecitabine should be taken with food or within 30 minutes after food.

The prescribing information for capecitabine must be consulted for guidance on dose delay and dose reduction recommendations for capecitabine.

TYKERB/letrozole Combination
The recommended dose of lapatinib is 1500 mg (i.e. six tablets) once daily every day when taken in combination with letrozole. TYKERB should be taken at least one hour before, or at least one hour after a low fat meal (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

When lapatinib is co-administered with letrozole, the recommended dose of letrozole is 2.5 mg once daily.

Cardiac events (see WARNINGS AND PRECAUTIONS).
TYKERB should be discontinued in patients with symptoms associated with decreased LVEF that are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or greater or if their LVEF drops below the institutions lower limit of normal. Consideration may be given to restarting TYKERB after a minimum of 2 weeks and only if the LVEF recovers to normal and the patient is asymptomatic. If TYKERB is restarted under these circumstances, a reduced dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with letrozole) is recommended. Based on current data, the majority of LVEF decreases occur within the first 12 weeks of treatment, but there is limited data on long term exposure.

Interstitial lung disease/pneumonitis (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS). TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or greater.

Diarrhea (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS)
TYKERB dosing should be interrupted in patients with diarrhea which is NCI CTCAE grade 3 or grade 1 or 2 with complicating features (moderate to severe abdominal cramping, nausea or vomiting greater than or equal to NCI CTCAE grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding or dehydration). TYKERB may be reintroduced at a lower dose (reduced from 1000 mg/day to 750 mg/day, from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day) when diarrhea resolves to grade 1 or less. TYKERB dosing should be permanently discontinued in patients with diarrhea which is NCI CTCAE grade 4.

Severe cutaneous reactions (see WARNINGS AND PRECAUTIONS) TYKERB should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions.

Renal Impairment
There is no experience of TYKERB in patients with severe renal impairment; however, patients with renal impairment are unlikely to require dose modification of TYKERB given that less than 2% of an administered dose (TYKERB and metabolites) is eliminated by the kidneys (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Hepatic Impairment
TYKERB is metabolised in the liver. Moderate and severe hepatic impairment have been associated respectively, with 56% and 85% increases in systemic exposure. Administration of TYKERB to patients with hepatic impairment should be undertaken with caution due to increased exposure to the drug. TYKERB dosing should be discontinued if changes in liver function are severe and patients should not be retreated. (see WARNINGS AND PRECAUTIONS and ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

There is no safety data from clinical trials on the use of TYKERB in patients with severe hepatic impairment (Child-Pugh Class C). TYKERB should be used with caution in these patients (see WARNINGS AND PRECAUTIONS and ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Concomitant Strong CYP3A4 Inhibitors
The concomitant use of strong CYP3A4 inhibitors should be avoided (See WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS). There are no clinical data recommending an appropriate dose adjustment in patients receiving strong CYP3A4 inhibitors. However, if patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered. 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.

Concomitant Strong CYP3A4 Inducers
The concomitant use of strong CYP3A4 inducers should be avoided (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS). There are no clinical data recommending an appropriate dose adjustment in patients receiving strong CYP3A4 inducers. If patients must be co-administered a strong CYP3A4 inducer the dose of TYKERB should be titrated gradually based on tolerability. If the strong inducer is discontinued the TYKERB dose should be reduced over approximately 2 weeks to the indicated dose.

Other toxicities
Discontinuation or interruption of dosing with TYKERB may be considered when a patient develops toxicity greater than or equal to grade 2 on the NCI CTCAE. Dosing can be restarted at either, 1250 mg/day when administered with capecitabine or 1500 mg/day when administered with letrozole, when the toxicity improves to grade 1 or less. If the toxicity recurs, then TYKERB should be restarted at a lower dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with letrozole).

Missed Dose
Missed doses of TYKERB should not be replaced and the dosing should resume with the next scheduled daily dose (see OVERDOSAGE).

Administration
TYKERB tablets are to be taken orally.

OVERDOSAGE

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or ErbB2 (HER2) tyrosine phosphorylation. The maximum oral dose of TYKERB that has been administered in clinical trials is 1800 mg once daily.

More frequent ingestion of TYKERB could result in serum concentrations exceeding those observed in clinical trials, therefore missed doses should not be replaced and dosing should resume with the next scheduled daily dose (see DOSAGE AND ADMINISTRATION). Continuous ECG monitoring may be appropriate in cases of overdose.

Symptoms and Signs
Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with TYKERB. Symptoms observed include known TYKERB associated adverse events *(see Adverse Reactions)*, and in some cases sore scalp, sinus tachycardia (with an otherwise normal ECG), and/or mucosal inflammation.

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

Further management should be as clinically indicated or as recommended by the Regional Poison Control Centre, where available.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Lapatinib ditosylate is a novel small molecule, dual 4-anilinoquinazoline kinase inhibitor with a unique mechanism of action, since it is a potent, reversible and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and of ErbB2 (HER2) receptors (estimated Ki^{app} values of 3nM and 13nM, respectively). Like other small-molecule tyrosine kinase inhibitors, lapatinib mimics adenosine triphosphate (ATP) and binds to the ATP binding site at the tyrosine kinase domain. As a result, lapatinib blocks ATP from binding to the tyrosine kinase domain and inhibits tyrosine kinase from using ATP as a cofactor for phosphorylation of tyrosine residues. Unlike other small molecule

tyrosine kinase inhibitors which only inhibit one type of intracellular tyrosine kinase domain, lapatinib inhibits two members of the human epidermal growth family, i.e. both ErbB1 and ErbB2 tyrosine kinase.

Lapatinib has a slow off-rate from these receptors (half-life greater than or equal to 300 minutes). This dissociation rate was found to be slower than other 4-anilinoquinazoline kinase inhibitors studied. Lapatinib inhibits ErbB-driven tumour cell growth *in vitro* and in various animal models.

In addition to its activity as a single agent, an additive effect was demonstrated in an *in vitro* study when lapatinib and 5-Fluorouracil (the active metabolite of capecitabine) were used in combination in the four tumour cell lines tested. The clinical significance of these *in vitro* data is unknown.

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 findings suggest non-cross-resistance between these two ErbB2 (HER2) directed agents.

Hormone sensitive breast cancer cells (estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) that co-express ErbB2 (HER2) tend to be resistant to established endocrine therapies. Hormone sensitive breast cancer cells that initially lack EGFR or ErbB2 (HER2) will up regulate these receptors as the tumour becomes resistant to endocrine therapy.

Cardiac Electrophysiology

QT Prolongation

The effect of lapatinib on the QT-interval was evaluated in a single-blind, placebo controlled, single sequence (placebo and active treatment) crossover study in patients with advanced solid tumors (N=58) (Study EGF114271). The majority of subjects (64%) were female. The median age was 56 years. During the 4-day treatment period, three doses of matching placebo were administered 12 hours apart in the morning and evening on Day 1 and in the morning on Day 2. This was followed by three doses of lapatinib 2000 mg administered in the same way. Measurements, including ECGs and pharmacokinetic samples were done at baseline and at the same time points on Day 2 and Day 4.

The primary endpoint of placebo-corrected least square mean change in Fridericia-corrected QT (QTcF) interval from Baseline ($\Delta\Delta$QTcF) at each time point was analysed in both the Evaluable Population (defined as subjects that received consecutive doses of study drug in the proper sequence as specified in the protocol and completed an adequate number of ECG acquisitions via Holter monitoring on Day 1 and through the 24-hour time point on Study Days 2/3 and 4/5) and the Pharmacodynamic (PD) population

(defined as subjects that received at least one dose of placebo or lapatinib and completed the ECG acquisition via Holter monitoring on at least one time point on Study Days 1, 2, 3 and 4). In the evaluable population (N=37), the maximum mean ΔΔQTcF of 8.75 ms (90% CI: 4.08, 13.42) was observed 10 hours after ingestion of the third dose of lapatinib 2000 mg. The ΔΔQTcF exceeded the 5 ms threshold and the upper bound 90% CIs exceeded the 10 ms threshold at multiple time points. The results for the PD population (n=52) were consistent with those from the evaluable population (maximum ΔΔQTcF of 7.91 ms, 90% CI: 4.13, 11.68) observed 10 hours after ingestion of the third dose of lapatinib. The PK/PD analyses confirmed the presence of a positive relationship between lapatinib plasma concentrations and ΔΔQTcF.

In an uncontrolled, open-label, dose escalation study in patients with solid tumours receiving TYKERB at doses of 175 mg/kg to 1800 mg/kg for 14 days, concentration-dependent prolongation of the QTc interval was observed. The magnitude of QTc prolongation at maximal plasma concentrations based on pharmacokinetic-pharmacodynamic modelling was predicted to be as follows:

Predicted Change from Baseline in QTc (ms) N=38					
Condition*	**Lapatinib concentration (ng/mL)**	**Machine Read ECG**		**Manually Read ECG**	
		mean slope	**95th percentile slope**	**mean slope**	**95th percentile slope**
Geometric mean C_{max} in EGF10005	3203	12	20	7	13
Maximum observed C_{max} in EGF10005	7487	27	47	16	29
Moderate** hepatic impairment (x 1.15)	3683	13	23	8	14
Ketoconazole inhibition (x 2.14)	6854	24	43	15	27
High-fat breakfast (x 3.15)	10089	36	63	22	39

$QTc=QT/RR^{0.33}$

* geom. mean C_{max} value multiplied by geom. mean ratio of effect noted in parentheses for each condition

** C_{max} was decreased in severe hepatic impairment so change due to moderate impairment is provided

Pharmacokinetics

Absorption: Absorption following oral administration of TYKERB is incomplete and variable (approximately 50 to 100% coefficient of variation in AUC). 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 1250 mg produces steady state geometric mean (95% confidence interval) C_{max} values of 2.43 (1.57 to 3.77) µg/mL and AUC values of 36.2 (23.4 to 56) µg*hr/mL.

Systemic exposure to lapatinib is increased when administered with food (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS). 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 (greater than 99%) to albumin and alpha-1 acid glycoprotein. *In vitro* studies indicate that lapatinib is a substrate for the transporters BCRP (ABCG2) and Pgp (ABCB1). Lapatinib has also been shown to inhibit *in vitro* to Pgp (IC_{50} 2.3 µg/mL), BCRP (IC_{50} 0.014 µg/mL) and the hepatic uptake transporter OATP 1B1 (IC_{50} 2.3 µg/mL), *in vitro* at clinically relevant concentrations. The clinical significance of these effects on the pharmacokinetics of other drugs or the pharmacological activity of other anti-cancer agents is not known. Lapatinib does not significantly inhibit the OAT or OCT renal transporters (*in vitro* IC_{50} values were greater than or equal to 6.9 µg/mL).

Metabolism: Lapatinib undergoes extensive metabolism, primarily by CYP3A4/5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which account for more than 14% of the dose recovered in the feces or 10% of lapatinib concentration in plasma.

TYKERB inhibits CYP3A4 (Ki 0.6 to 2.3 µg/mL) and CYP2C8 (0.3 µg/mL) *in vitro* at clinically relevant concentrations. TYKERB did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, and CYP2D6 or UGT enzymes (*in vitro* IC_{50} values were greater than or equal to 6.9 µg/mL).

In healthy volunteers receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure to lapatinib was increased approximately 3.6–fold, and half-life increased 1.7–fold (see DRUG INTERACTIONS, Drug-Drug interaction).

In healthy volunteers receiving carbamazepine, a CYP3A4 inducer, at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, systemic exposure to lapatinib was decreased by approximately 72% (see DRUG INTERACTIONS, Drug-Drug interaction).

Excretion: The half-life of lapatinib measured after single dose increases with increasing dose. However, daily dosing of TYKERB results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. Lapatinib is predominantly eliminated through metabolism by CYP3A4/5. The primary route of elimination for lapatinib and its metabolites is in feces (median recovery 27% (range 3 to 67%)). Less than 2% is excreted in urine.

Special Populations and Conditions

Hepatic Insufficiency: The pharmacokinetics of TYKERB were examined in subjects with moderate (n = 8) or severe (n = 4) hepatic impairment and in 8 healthy control subjects. Systemic exposure (AUC) to lapatinib after a single oral 100 mg dose increased approximately 56% and 85% in subjects with moderate and severe hepatic impairment, respectively. Administration of TYKERB in patients with hepatic impairment should be undertaken with caution due to increased exposure to the drug. There is no safety data from clinical trials on the use of TYKERB in patients with severe hepatic impairment, however based on pharmacokinetic modeling, a dose reduction is recommended although the safety and efficacy of this dose has not been demonstrated (See DOSAGE and ADMINISTRATION, Recommended Dose and Dosage Adjustment). In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with lapatinib (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Renal Insufficiency: TYKERB pharmacokinetics have not been specifically studied in patients with renal impairment or in patients undergoing hemodialysis. However, renal impairment is unlikely to affect the pharmacokinetics of TYKERB given that less than 2% of an administered dose (as unchanged lapatinib and metabolites) is eliminated by the kidneys.

STORAGE AND STABILITY

Store between 15-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TYKERB tablets, 250 mg, are yellow, oval, biconvex, film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

The inactive ingredients of TYKERB are: **Tablet Core**: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate; **Coating**: hypromellose, iron oxide red, iron oxide yellow, macrogol/PEG 400, polysorbate 80 and titanium dioxide.

TYKERB film-coated tablets are available in HDPE bottles of 70 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

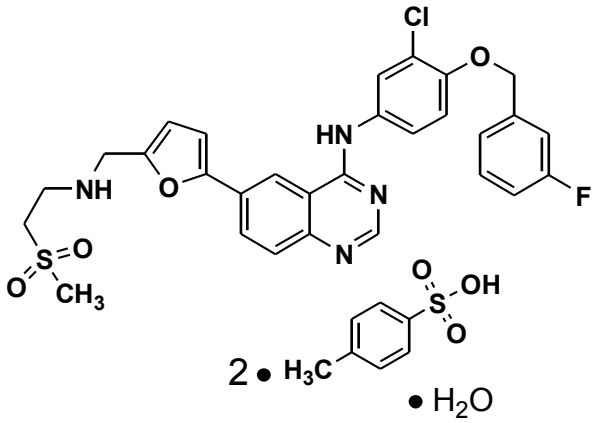
Common name: lapatinib ditosylate

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

Molecular formula: $C_{29}ClFH_{26}N_4O_4S$ $(C_7H_8O_3S)_2$ H_2O (ditosylate monohydrate)

Molecular mass: 943.5 (581.07 free base)

Structural formula:



Physicochemical properties: 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.

The 250 mg tablets contain 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet.

CLINICAL TRIALS

Data have shown that in some settings TYKERB is less effective than trastuzumab based treatment regimens.

TYKERB/capecitabine Combination

Study demographics and trial design

The efficacy and safety of TYKERB (lapatinib ditosylate) tablets in combination with capecitabine in breast cancer were evaluated in one open-label randomized, phase III trial. Patients eligible for enrolment had ErbB2 (HER2) over-expressing (IHC 3+, or IHC 2+ and FISH positive), and locally advanced or metastatic breast cancer, progressing after prior treatment that included taxanes, anthracyclines and trastuzumab. Table 5 summarizes the demographic and disease characteristics of the two study groups.

Patients were randomized to receive either TYKERB 1250 mg once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or to receive capecitabine alone (2500 mg/m^2/day on days 1-14 every 21 days). Study treatment was given until disease progression, or withdrawal for another reason. The primary endpoint was time to progression (TTP) including deaths due to breast cancer, as assessed by an independent review committee (IRC). The study was halted based on the results of a pre-specified interim analysis that showed an improvement in TTP for patients receiving TYKERB plus capecitabine. An additional 75 patients were enrolled in the study between the time of the interim analysis and the updated analysis on April 3, 2006. At this time patients receiving capecitabine alone were permitted to cross over to the study arm and receive TYKERB. After the study was halted, 36 patients crossed over from capecitabine to TYKERB plus capecitabine, of whom 26 crossed over prior to disease progression while on capecitabine alone.

Table 5 Demographic and Disease Characteristics

Characteristics	TYKERB + Capecitabine N = 198	Capecitabine N = 201
Age, Years		
Median (range)	54 (26-80)	52 (28-83)
Age Group, %		
< 65 years	83	88
≥ 65 years	17	12
Race, %		
White	91	90
Asian	3	4
Hispanic	2	3
Black	3	1
Other	1	1
Stage & Site of Disease at Study Entry, %		
IIIb or Stage IIIc with T4 lesion	4	4
IV – visceral	75	79
IV – non-visceral	22	17
Hormone Receptor Status, %		
ER+ and/or PR+	48	46
ER- and PR-	48	50
unknown	4	3

ER = estrogen receptor
PR = progesterone receptor

The efficacy analyses of April 3, 2006 are shown in Table 6.

Study results

At the updated analysis, the IRC and investigator data demonstrated that lapatinib in combination with capecitabine significantly increased time to progression compared to capecitabine alone. However, the IRC and investigator assessments of TTP were discordant (the IRC analysis of TTP was likely overestimated), thus the magnitude of improvement in TTP cannot be quantified in this trial. Although unblinded investigator's results are often affected by assessment bias, the investigator's results in this trial are considered a more accurate assessment of TTP.

Table 6 Efficacy Results* at the time of the updated analysis (April 3, 2006)

	Investigator Assessment		Independent Assessment	
	TYKERB plus capecitabine	**Capecitabine alone**	**TYKERB plus capecitabine**	**Capecitabine alone**
	(N = 198)	(N = 201)	(N = 198)	(N = 201)
Number of TTP events	121	126	82	102
Median TTP, weeks (25^{th}, 75^{th} percentile), weeks	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)
Hazard Ratio (95% CI) p value	0.72 (0.56, 0.92) 0.00762		0.57 (0.43, 0.77) 0.00013	
Response Rate (%)	31.8	17.4	23.7	13.9
(95% CI)	(25.4, 38.8)	(12.4, 23.4)	(18.0, 30.3)	(9.5, 19.5)

*There was a consistent benefit in TTP by both investigator and independent assessment, although the magnitude of TTP by independent assessment was likely overestimated.

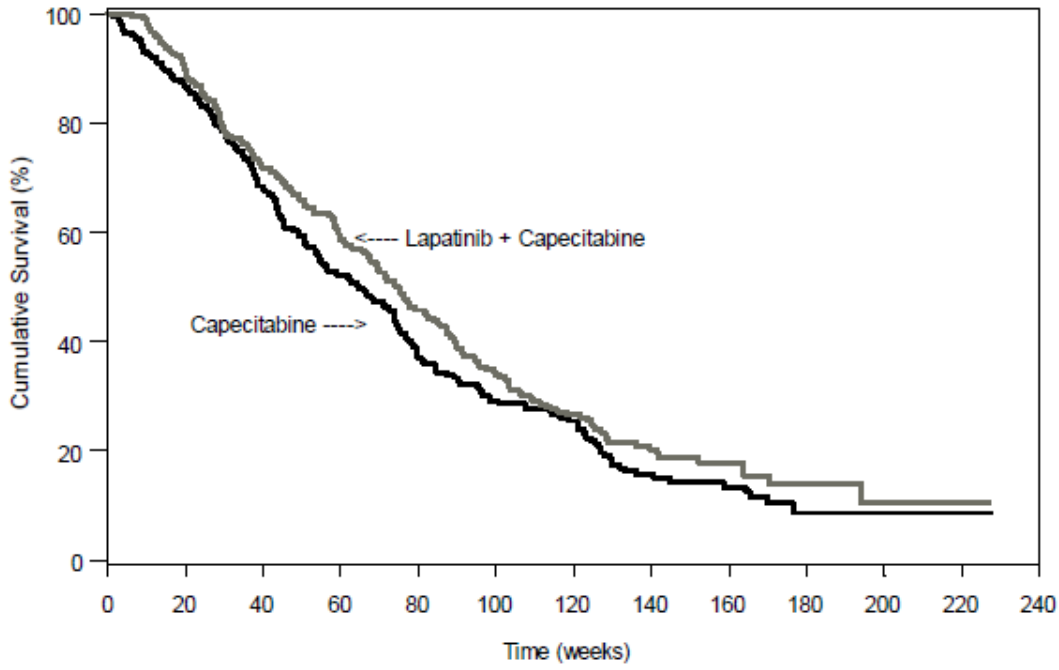
TYKERB when given in combination with capecitabine significantly prolonged the progression free survival compared to capecitabine alone. In addition, on the combination arm, there were 4 (2%) progressions in the central nervous system as compared with 13 (6%) progressions on the capecitabine alone arm (p=0.0445). However, a statistically significant overall survival advantage, or palliation due to therapy has not been demonstrated. The most recent analysis of overall survival to October 1, 2008 demonstrates an unadjusted hazard ratio of 0.87 (95% CI: 0.71 1.08, p=0.210). The median overall survival is 64.7 weeks for capecitabine alone compared to 75.0 weeks for lapatinib + capecitabine (Table 7).

Table 7 Summary of Overall Survival (ITT Population) (October 1, 2008)

	TYKERB plus Capecitabine N=207*	**Capecitabine N=201***
Subject deaths, n (%) Died	168 (81)	172 (86)
Kaplan-Meier estimate of Overall Survival, weeks Median, [95% CI]	75.0 [65.3,85.6]	64.7 [53.3,74.4]
Hazard ratio Estimate, [95% CI]	0.87 [0.71,1.08]	
Log-rank two-sided p-value	0.210	

*At the time of enrolment was halted to EGF100151 (April 3, 2006), 399 patients were randomized to study therapy and 9 other patients were being screened. All 9 patients in screening, and all those already receiving capecitabine monotherapy, were offered combination treatment. In total, 207 patients were assigned to the combination therapy and 201 patients were assigned to capecitabine monotherapy.

Figure 1 **Kaplan-Meier Estimates of Overall Survival: ITT Population (October 1, 2008)**



TYKERB/letrozole Combination

TYKERB has been studied in combination with letrozole for the treatment of advanced or metastatic breast cancer in hormone receptor positive (estrogen receptor [ER] positive and / or progesterone receptor [PgR] positive) postmenopausal women.

EGF30008 was a randomized, double-blind, controlled trial in patients with hormone-sensitive (HS) locally advanced or metastatic breast cancer (MBC), who had not received prior therapy for their metastatic disease. The objective was to evaluate and compare progression free survival (PFS) in subjects with ER positive and/or PgR positive, ErbB2 (HER2) positive advanced or metastatic breast cancer treated with lapatinib and letrozole versus letrozole and placebo. The primary endpoint was investigator-evaluated PFS in the ErbB2 (HER2) positive population. 1286 patients were randomized to TYKERB 1500 mg once daily plus letrozole 2.5 mg once daily or letrozole with placebo. Randomisation was stratified by sites of disease and prior adjuvant anti-estrogen therapy. ErbB2 (HER2) receptor status was retrospectively determined by central laboratory testing. Of all patients randomized to treatment, 219 patients (17%) had tumours over-expressing the ErbB2 (HER2) receptor (the 'ErbB2 (HER2) positive population', IHC 3+, or IHC 2+ and FISH positive), which was the pre-specified primary population for the analysis of efficacy. There were 952 ErbB2 (HER2) negative patients (74%) and a total of 115 patients (9%) whose ErbB2 (HER2) status was unconfirmed.

The baseline demographic and disease characteristics were balanced between the two treatment arms and are provided in Table 8 for the ErbB2 (HER2) positive population.

Table 8 Baseline Deomographic and Disease Characteristics ErbB2 (HER2) positive Population

Characteristics	TYKERB + Letrozole N = 111	Letrozole N = 108
Age, Years		
Median (range)	60.0 (44-85)	59.0 (45-87)
Age Group, %		
< 65 years	63	66
≥ 65 years	37	34
Race, %		
White	74	84
Asian	11	5
Hispanic	13	8
Black	2	3
Other	<1	0
Centrally Confirmed Hormone Receptor Status, %		
ER+ or PR+	84	85
ER- and PR-	9	6
Unknown	7	8
Median time since 1st diagnosis of breast cancer (months)	29.2	27.8
Histology at 1st diagnosis, %		
Infiltrating ductal	86	81
Lobular Invasive	10	10
Other[a]	4	9
Stage of Disease at Study Entry, %		
IIIB /IIIC	5	6
IV	95	94
Involved Site (Strata), %		
Visceral	86	83
Bone Only	14	17

ER = estrogen receptor
PR = progesterone receptor
a) Included tubular, adenocystic, carcinosarcoma, other.

In the ErbB2 (HER2) positive population (N=219), investigator-determined progression-free survival (PFS) was significantly greater with TYKERB plus letrozole (N=111) compared with letrozole plus placebo (N=108) (see Table 9 and Figure 2). The median duration of treatment in the ErbB2 (HER2) positive population was 32.57 weeks for the TYKERB plus letrozole group and 13.86 weeks for the letrozole plus placebo group. The majority (53% vs 67%) of PFS events occurred in the first 3 assessments (12, 24 and 36 weeks) for the combination and letrozole arms, respectively.

Table 9 Efficacy results from Study EGF30008 (TYKERB/letrozole)

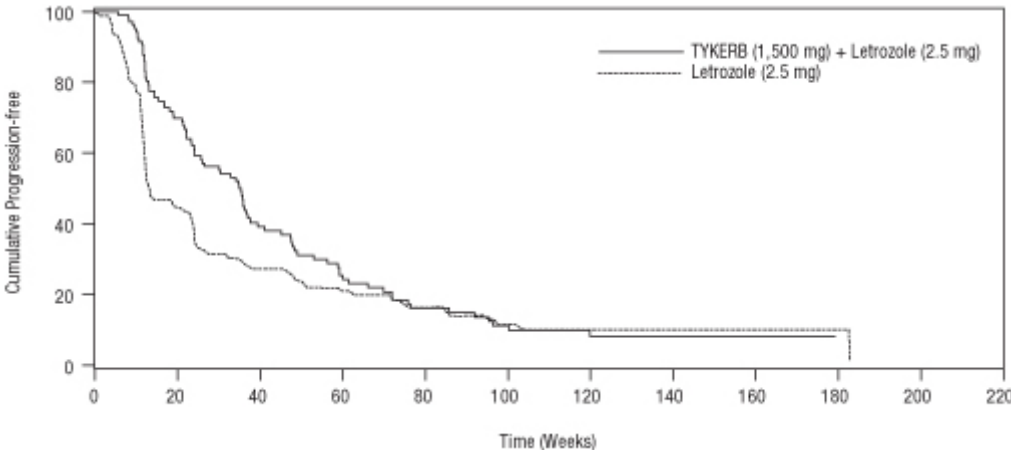
	ErbB2 (HER2) Positive Population		ErbB2 (HER2) Negative Population	
	TYKERB 1500 mg/day + Letrozole 2.5 mg/day	**Letrozole 2.5 mg /day**	**TYKERB 1500 mg/day + Letrozole 2.5 mg/day**	**Letrozole 2.5 mg /day**
	N = 111	**N = 108**	**N = 478**	**N = 474**
Median PFS[a], weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)	59.7 (48.6, 69.7)	58.3 (47.9, 62.0)
Hazard Ratio *P* value	0.71 (0.53, 0.96) 0.019		0.90 (0.77, 1.05) 0.188	
PFS Cox Regression Treatment Hazard Ratio *P* value	0.65 (0.47, 0.89) 0.008		0.77 (0.64, 0.94) 0.010	
Response Rate (%) (95% CI)	27.9 (19.8, 37.2)	14.8 (8.7, 22.9)	32.6 (28.4, 37.0)	31.6 (27.5, 36.0)
CBR[b] (%) (95% CI)	47.7 (38.2, 57.4)	28.7 (20.4, 38.2)	58.2 (53.6, 62.6)	56.5 (51.9, 61.1)
Median OS, weeks (95% CI)	144.7 (95.6, NE)	140.3 (92.1, 159.4)	174 .4 (161.1, NE)	179.7 (168.9, NE)
OS Hazard Ratio *P* value	0.74 (0.5, 1.1) 0.113		1.15 (0.9, 1.4) 0.193	

PFS = progression-free survival; CI = confidence interval; OS = overall survival; NE = Not evaluable. ErbB2 (HER2) overexpression = IHC 3+, or IHC 2+ and FISH positive; ErbB2 (HER2) negative = IHC 0, 1+ or 2+ and/or FISH negative.

a. Kaplan-Meier estimate.

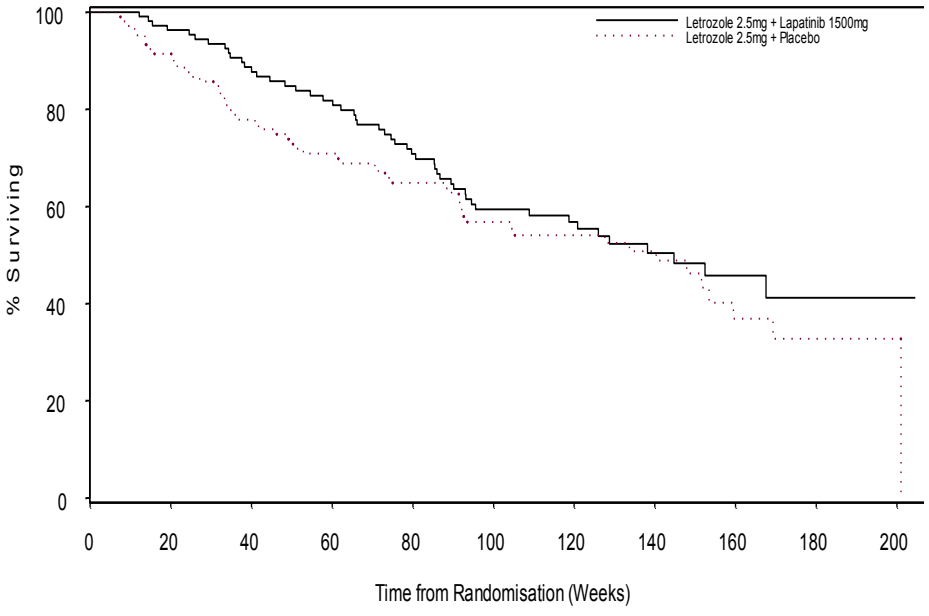
b. CBR = Clinical Benefit Rate in patients with evidence of confirmed complete response, partial response, or stable disease for at least 6 months (≥183 days)

Figure 2 Kaplan-Meier Estimates for Progression-Free Survival for the ErbB2 (HER2) Positive Population in Study EGF30008



To further explore the impact of baseline prognostic factors on PFS in the TYKERB plus letrozole group compared with letrozole alone, a pre-planned Cox regression analysis was performed which also favoured the combination arm (HR=0.65 (95% CI 0.47-0.89) p=0.008). In addition to a PFS benefit seen in the ErbB2 (HER2) positive patient population, combination therapy of TYKERB and letrozole offered an improvement in objective response rate compared with letrozole treatment alone (27.9% and 14.8% respectively) and in Clinical Benefit Rate (CBR) (47.7% and 28.7% respectively). The overall survival (OS) data were not mature, with 47% of the events having occurred; however, a trend in OS in favour of the TYKERB plus letrozole in the ErbB2 (HER2) positive population was observed (Table 9, Figure 3).

Figure 3 Kaplan-Meier Estimate Overall Survival for the ErbB2 (HER2) Positive Population in Study EGF30008



Subjects At Risk											
Letrozole 2.5mg + Lapatinib 1500mg	111	104	92	82	69	51	42	26	15	7	2
Letrozole 2.5mg + Placebo	108	96	78	71	61	46	35	27	10	6	1

In the ErbB2 (HER2)-negative population (N=952), no significant differences in PFS were observed between treatment arms (Table 9). The OS data were not mature at the time of reporting with 34% of the events having occurred, however, a trend towards a potential decrease in OS was observed in the TYKERB plus letrozole arm (Table 9).

DETAILED PHARMACOLOGY

Refer to PART I, ACTIONS AND CLINICAL PHARMACOLOGY

TOXICOLOGY

Single-dose toxicity

The approximate non-lethal oral dose of lapatinib in mice and rats is > 2000 mg/kg (maximum dose tested). This dose is approximately 8 and 16 times the recommended adult human dose of 1250 mg/day in mice and rats, respectively.

Repeat-dose toxicity

The chronic toxicity profile of lapatinib was evaluated in a series of oral repeated-dose studies up to 26 weeks in rats at doses of 20, 60 and 180 (males) or 120 (females) mg/kg/day, and 39 weeks in dogs at doses of 10, 40 and 100 mg/kg. The totality of the data indicates that the target organs of lapatinib toxicity are liver, GI tract, and skin. The doses associated with toxicity are similar to the expected human clinical exposure.

Combination toxicity

TYKERB is indicated in combination with capecitabine. Several target organs of toxicity for capecitabine and lapatinib are similar and include skin, GI tract and liver. In clinical trials, an increased incidence of adverse events is noted for patients treated with TYKERB + capecitabine when compared with capecitabine alone, suggesting the potential for enhanced toxicity (see PART I, ADVERSE REACTIONS). A toxicology study was not conducted to evaluate if cumulative organ toxicity is observed following administration of lapatinib in combination with capecitabine.

Mutagenicity and clastogenicity

Lapatinib was not clastogenic or mutagenic in a battery of assays including the Chinese hamster chromosome aberration assay, the Ames assay, human lymphocyte chromosome aberration assay and an *in vivo* rat bone marrow chromosome aberration assay.

Carcinogenicity

A two-year mouse carcinogenicity study was conducted wherein males and females were administered lapatinib at doses of 75, 150 and 300 mg/kg/day. Increased mortality was observed in males at 150 and 300 mg/kg/day and in females at 300 mg/kg/day, and was related to skin toxicities. Due to early sacrifice of males dosed at 300 mg/kg/day, assessment of carcinogenic potential in this group was not performed. There was no evidence of carcinogenicity in males and females at doses up to 150 and 300 mg/kg/day, respectively (2 times the expected human clinical exposure).

A two-year rat carcinogenicity study was conducted wherein males were administered lapatinib at 60, 120, 240 and 500 mg/kg/day and females were administered lapatinib 20, 60, 180 and 300 mg/kg/day. Increased mortality was observed in males at 500 mg/kg/day and females at 300 mg/kg/day, and was related to skin toxicities. Renal infarcts and papillary necrosis was observed in females from 60 mg/kg/day (7 times the expected clinical exposure) and 180 mg/kg/day (10 times the expected clinical exposure), respectively. An increased incidence of benign hemangioma of the mesenteric lymph nodes was noted in males from 120 mg/kg/day (1 times the expected clinical exposure)

and in females at 180 mg/kg/day (10 times the expected clinical exposure) but was within background range. The clinical significance of these findings to humans is not known.

Reproduction

There were no effects on male or female rat gonadal function, mating, or fertility at doses up to 120 mg/kg/day (females) and up to 180 mg/kg/day (males) (8 and 3times the expected human clinical exposure, respectively). The effect on human fertility is unknown.

Development

Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60, and 120 mg/kg/day. There were no teratogenic effects. In rats, minor anomalies (left-sided umbilical artery, cervical rib and precocious ossification) occurred at the maternally toxic dose of 120 mg/kg/day (8 times the expected human clinical exposure). In rabbits, lapatinib was associated with maternal toxicity at 60 and 120 mg/kg/day (0.08 and 0.23 times the expected humanclinical exposure, respectively) and abortions at 120 mg/kg/day. At maternally toxic doses, decreased fetal body weights, decreased number of live fetuses and minor skeletal variations were noted. The developmental no adverse effect level was considered to be 60 mg/kg/day in rats and 30 mg/kg/day in rabbits (4 and 0.03 times the expected human clinical exposure, respectively).

In the rat pre- and postnatal development study, a decrease in pup survival occurred between birth and postnatal day 21 at 60 and 120mg/kg/day. The highest no-effect dose for this study was 20 mg/kg/day (3 times the expected human clinical exposure).

SAFETY PHARMACOLOGY

The effect of lapatinib on hERG tail currents was studied in stably transfected HEK-293 cells. Lapatinib inhibited hERG channel tail currents in a concentration-dependent manner when compared with vehicle (N=5-6 cells/concentration). The IC_{25} and IC_{50} values were estimated to be 0.181 and 1.11 µM (0.1052 and 0.6450 µg/mL), respectively. The IC_{25} and IC_{50} values are 4.3 fold and 26.5 fold, respectively, the human free C_{max} obtained with a 1250 mg/day oral dose of TYKERB (0.0243 g/mL; based on 99% protein binding).

No treatment-related effects were noted on action potential parameters in isolated canine cardiac Purkinje fibres following treatment with lapatinib at concentrations up to 2.56 µg/mL.

In conscious telemetered male beagle dogs (N=4), cardiovascular function was assessed in a crossover study investigating single oral doses of 0, 50, 150, and 500 mg/kg. Higher mean systolic, diastolic, and mean arterial blood pressure were noted after 150 and 500 mg/kg compared to controls, after approximately 10 to 14 or 6 to 14 hours, respectively. The no adverse effect level for the study was 50 mg/kg. No effects on ECG interval parameters were observed.

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PART III: CONSUMER INFORMATION

PrTYKERB®
Lapatinib tablets
(as lapatinib ditosylate)

This leaflet is part III of a three-part "Product Monograph" published when TYKERB® (lapatinib ditosylate) tablets were approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TYKERB. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TYKERB is used in combination with capecitabine for the treatment of patients with metastatic breast cancer that is ErbB2 (HER2) positive. The combination treatment is indicated for women whose breast cancer has progressed after treatment with a taxane, and an anthracycline. In addition, their metastatic breast cancer should have progressed during treatment with trastuzumab.

TYKERB in combination with capecitabine has been shown to delay progression of breast cancer. It has not been proven to increase your survival or reduce the symptoms associated with your breast cancer.

TYKERB is used in combination with letrozole for the treatment of post-menopausal patients with hormone receptor positive metastatic breast cancer, whose tumours overexpress the ErbB2 (HER2) receptor, and who are suitable for endocrine therapy.

What it does:
TYKERB is a kinase inhibitor which interferes with the growth of certain tumour cells.

When it should not be used:
TYKERB must not be used if you are allergic to lapatinib ditosylate, or any of the other ingredients in TYKERB (see *What the important nonmedicinal ingredients are*).

What the medicinal ingredient is:
Lapatinib ditosylate monohydrate.

What the important nonmedicinal ingredients are:
TYKERB tablets contain the following nonmedical ingredients: hypromellose, iron oxide red, iron oxide yellow, macrogol/PEG 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

What dosage forms it comes in:
TYKERB is provided as a yellow, oval, biconvex film-coated tablet with "GS XJG" engraved on one side.

Each tablet contains 250 mg lapatinib as lapatinib ditosylate monohydrate.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
TYKERB should be prescribed and managed by a doctor experienced in anticancer drugs. Serious side effects of TYKERB include:
- Liver toxicity can be severe and deaths have happened (harmful effect on the liver)
- Decreased left ventricular ejection fraction (decreased pumping of blood from the left ventricle of the heart)
- Abnormal heartbeat (QT prolongation)
- Severe diarrhea, which can be life-threatening

BEFORE you use TYKERB, talk to your doctor or pharmacist if:
- You have or have had heart problems, such as abnormal heartbeat (arrhythmias or dysrhythmias) or fainting spells
- You have electrolyte disturbances, such as low blood potassium, low blood magnesium, low blood calcium, or conditions that could lead to electrolyte disturbances such as eating disorder, vomiting, diarrhea, dehydration, diabetes (with nerve disorders)
- You have a family history of sudden cardiac death at younger than 50 years of age
- You have lung problems
- You have liver problems
- You have diarrhea or any changes in bowel patterns
- You are pregnant, or are planning to become pregnant
- You are breastfeeding or are planning to do so

TYKERB may cause harm to your unborn baby. Therefore, you should use effective methods of contraception while taking TYKERB and for at least 5 days after stopping TYKERB. Ask your doctor about effective contraception options. If you become pregnant during treatment with TYKERB, tell your doctor immediately. It is not known whether TYKERB passes into breast milk, therefore do not breast-feed while taking TYKERB and for 5 days after the last dose as it may harm your baby.

TYKERB has an effect on the electrical activity of the heart known as QT/QTc prolongation. This may lead to disturbances in the heartbeat (heart rhythm) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting (syncope) or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart problems, taking medicines that affect the heart, being female or being over 65 years of age. It is important to follow the instructions of your doctor with regard to dosing or any special tests. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should seek immediate medical attention.

Safety and efficacy of TYKERB have not been established in children.

TYKERB can make you feel drowsy or sleepy.

- Don't drive or use machines unless you are sure you are not affected.

Severe Skin Reactions
Severe skin reactions have been seen with TYKERB. Symptoms may include skin rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever or any combination of these. Tell your doctor as soon as possible if you get any of these symptoms. As severe skin reactions can be life threatening, your doctor may tell you to stop taking TYKERB.

TYKERB may increase the risk of photosensitivity. You are encouraged to avoid exposure to sunlight and apply broad spectrum sunscreens with an SPF ≥30 if exposure to sunlight cannot be avoided.

INTERACTIONS WITH THIS MEDICATION

There are certain groups of medicines that interact with TYKERB. The following list includes some, but not all, medicines that interact with TYKERB. Tell your doctor or pharmacist if you're taking any other medicines, if you've taken any recently, or if you start taking new ones. This includes non-prescription medicines, vitamins, and natural health products.

- drugs used to treat infections (antibiotics and anti-fungals)
- drugs used to treat HIV (AIDS)
- drugs used to treat chronic inflammation or asthma (steroids)
- drugs used to treat seizures (anticonvulsant drugs)
- drugs used to treat certain heart disorders and high blood pressure (calcium channel blockers)
- water pills (diuretics)
- opioids (e.g. methadone)
- antidepressants
- antipsychotics
- drugs that decrease stomach acidity (used to treat stomach ulcers or indigestion)
- herbal products (St. John's Wort)

You should also avoid grapefruit juice or products containing grapefruit juice.

Because TYKERB is given with another drug, either capecitabine or letrozole, you should also discuss with your doctor any medicines that should be avoided when taking capecitabine (Xeloda*) or letrozole.

Ask your health professional for advice before taking any medicine if you are unsure.

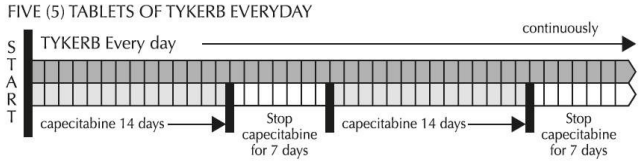
PROPER USE OF THIS MEDICATION

Always take TYKERB exactly as your doctor has told you. You should check with your doctor if you are not sure.

Usual dose:

TYKERB/capecitabine Combination
Five TYKERB tablets (a total dose of 1250 mg) once daily continuously in combination with capecitabine.

If you are prescribed TYKERB in combination with capecitabine, your doctor will advise you of the dose of capecitabine and when to take it. TYKERB AND CAPECITABINE TABLETS ARE SIMILAR IN COLOUR AND SIZE. THEREFORE, IT IS VERY IMPORTANT THAT YOU LOOK CLOSELY AT YOUR TABLETS AND IDENTIFY THEM CORRECTLY BEFORE YOU TAKE THEM TO AVOID CONFUSION. Refer also to "**What dosage forms it comes in"** above.



TYKERB/letrozole Combination
Six TYKERB tablets (a total dose of 1500 mg) once daily continuously with letrozole.

If you are prescribed TYKERB in combination with letrozole, your doctor will advise you about the dose of letrozole, when to take it and how often.

How to take:
Swallow the tablets whole with water.
TYKERB should be taken at least one hour before or at least

one hour after a low fat meal.
TYKERB tablets should be taken at about the same time each day.
Do not drink grapefruit juice while you are taking TYKERB.

If you have any problems/questions regarding the use of TYKERB, please consult with your health professional.

Overdose:
Dosage directions should be followed carefully. Never exceed the prescribed dose.

If you have accidentally taken more TYKERB tablets than you should, contact your doctor, or poison control centre, or go to the emergency room of the nearest hospital.

Missed Dose:
Do not take a double dose to make up for a forgotten dose on a given day, simply resume your dosing with the next scheduled dose the following day. If you have further questions on the use of TYKERB, ask your health professional.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TYKERB can cause side effects. Most of the side effects are mild to moderate. **Tell your doctor or pharmacist** if any of the side effects listed becomes **severe or bothers you,** or if you notice any side effects not listed in this leaflet**.**

Side effects of TYKERB in combination with capecitabine (XELODA®) or letrozole (FEMARA®) include:

Very common side effects:
These side effects may affect more than 10 in every 100 patients.
- Diarrhea (which if severe can be life-threatening), contact your doctor immediately at the first sign of diarrhea (loose stool), to treat it right away. Also tell your doctor immediately if your diarrhea worsens.
- Loss of appetite
- Indigestion or stomach/abdominal pain
- Feeling or being sick (nausea or vomiting)
- Constipation
- Tiredness
- Unusual hair loss or thinning
- Nose bleed
- Difficulty breathing
- Sore mouth or mouth ulcers
- Trouble sleeping (insomnia)
- Back pain or pain in extremities
- Rash or dry skin
- A skin reaction or pain on the palms of the hands or soles of the feet (including tingling, numbness, pain, swelling or reddening)

Supportive skin care regimens are available. Please talk to your healthcare provider for guidance.

Common side effects:
These side effects may affect between 1 to 10 in every 100 people.
- An effect on how your heart works – this may cause an irregular heartbeat and shortness of breath
- Headache
- Fever
- Swelling in extremities
- Pain in joints or bones
- Nosebleed
- Nail disorders – such as tender infection and swelling of the cuticles

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, fainting, or seizures, **you should seek immediate medical attention**.

Uncommon side effects:
These side effects may affect up to 1 in every 100 people.
- Liver problems – this may cause itching, yellow eyes or skin (jaundice), dark urine or pain or discomfort in the right upper area of the stomach.
- Swelling or inflammation of the lungs – this may cause coughing or shortness of breath.

Tell your doctor immediately if you get any of these symptoms. These symptoms may persist after you stop taking TYKERB.

Rare side effects:
These side effects may affect up to 1 in every 1000 people.
- Severe allergic reactions – symptoms may include: skin rash (including itchy, bumpy rash); unusual wheezing or difficulty in breathing; swollen eyelids, lips or tongue; pains in muscles or joints; collapse or blackout.

Tell your doctor immediately if you get any of these symptoms and do not take any more tablets.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	diarrhea		✓	
Common	Heart problems, which may cause: irregular heartbeat shortness of breath		 ✓	✓
Uncommon	Liver problems Lung inflammation (interstitial lung disease)		✓ ✓	
Rare	Severe allergic reactions			✓
Unknown	Severe skin reactions (symptoms may include blistering of the lips, eyes or mouth, skin peeling, fever or any combination of these)			✓

This is not a complete list of side effects. For any unexpected effects while taking TYKERB, contact your doctor or pharmacist.

HOW TO STORE IT

- Store between 15-30°C.
- Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novartis.ca or by contacting the sponsor,
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.,
Dorval, Quebec
H9S 1A9
1-800-363-8883

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