TYKERB™
(Lapatinib Ditosylate)
250 mg film coated tablets

Tradename

Tykerb™ Film-coated tablets 250 mg lapatinib

Description and composition

TYKERB film-coated tablets contain lapatinib ditosylate which is a member of 4-anilinoquinazoline class of kinase inhibitors. The chemical name for (IUPAC) lapatinib ditosylate is N-(3-chloro-4-{[(3-fluorophenyl) methyl]oxy}phenyl)-6-[5- ({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate. lapatinib

Lapatinib ditosylate monohydrate 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

Excipients

Yellow Film-coated Tablets

Microcrystalline cellulose

Povidone K30

Sodium starch glycolate (Type A)

Magnesium stearate

Hypromellose

Titanium dioxide

Macrogol 400

Polysorbate 80

Iron oxide red (C177491)

Iron oxide yellow (C177492)

Clinical pharmacology

Pharmacotherapeutic group, ATC

Human epidermal growth factor receptor 2 (HER)2 tyrosine kinase inhibitor, L01EH01.

Mechanism of action (MOA)

Tykerb is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 (ErbB2) receptors (estimated Kiapp values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life ≥ 300 minutes). This dissociation rate from ErbB1 was found to be slower for Tykerb than for erlotinib and gefitinib. Tykerb inhibits tumour cell proliferation in vitro, and inhibits the growth of ErbB1 (EGFR) and HER2 over-expressing xenograft tumours in mice. Inhibition of tumour growth was associated with decreased phosphorylation of ErbB1 (EGFR) and HER2 in tumour tissue.

The growth inhibitory effects of Tykerb were evaluated in trastuzumab-conditioned cell lines. Tykerb retained significant activity against breast cancer cell lines selected for resistance to trastuzumab by long-term growth in trastuzumab-containing medium *in vitro*. These findings suggest non-cross-resistance between these two ErbB2-directed agents.

Hormone sensitive breast cancer cells (oestrogen receptor [ER] positive and / or progesterone receptor [PgR] positive) that co-express ErbB2 tend to become resistant to established endocrine therapies. Hormone sensitive breast cancer cells initially lack ErbB1 or ErbB2 will upregulate these receptors as the tumour becomes resistant to endocrine therapy. Randomized trials in hormone sensitive metastatic breast cancer indicate that an ErbB2 or ErbB1 tyrosine kinase inhibitor may potentially improve clinical efficacy when added to endocrine therapy.

Pharmacodynamics (PD)

Cardiac electrophysiology

QT prolongation

Study EGF114271

The effect of Tykerb on the QTc-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). During the 4-day treatment period, 3 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 3 doses of 2000 mg Tykerb 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.

In the evaluable population (N=37), the maximum mean ΔΔQTcF (90% CI) of 8.75 ms (4.08, 13.42) was observed 10 hours after ingestion of the third dose of 2000mg Tykerb. 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 (90% CI) of 7.91 ms (4.13, 11.68) observed 10 hours after ingestion of the third dose of Tykerb. The PK/PD analyses confirmed a positive relationship between Tykerb plasma concentrations and ΔΔQTcF.

Pharmacokinetics (PK)

Absorption

Absorption of Tykerb following oral administration of Tykerb is highly variable. Serum concentrations appear after a median lag time of 0.25 hours (range 0 to 1.5 hours). Peak plasma concentrations (C_{max}) of Tykerb are achieved approx. 4 hours after administration. Daily dosing of 1250 mg produces steady state geometric mean (95% CI) 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/m. The absolute bioavailability of Tykerb has not been determined.

Systemic exposure to Tykerb is increased when administered with food (see Dosage regimen and administration and Interactions). Tykerb AUC values were approx. 3- and 4-fold higher (C_{max} approx. 2.5 and 3-fold higher) when administered with a low fat (5% fat [500 calories]) or high fat (50% fat [1,000 calories]) meal, respectively.

Distribution

Tykerb is highly bound (>99%) to albumin and alpha-1-acid glycoprotein. *In vitro* studies indicate that Tykerb is a substrate for the transporters BCRP (ABCG2) and p-glycoprotein (ABCB1). Tykerb has also been shown to inhibit 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. Tykerb does not significantly inhibit the OAT or OCT renal transporters (*in vitro* IC_{50} values were ≥6.9 µg/mL).

Biotransformation/metabolism

Tykerb undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, 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 faeces or 10% of the Tykerb concentration in plasma.

Elimination

The half-life of Tykerb measured after single doses 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 about 1 day. The primary route of elimination for Tykerb and its metabolites is in faeces, with less than 2% of the dose (as Tykerb and metabolites) excreted in urine. Recovery of unchanged Tykerb in faeces accounts for a median 27% (range 3 to 67%) of an oral dose.

In vitro evaluation of drug interaction potential

Tykerb inhibits CYP3A (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 (*in vitro* IC50 values were ≥6.9 μg/mL)

Special Patient Populations

Pediatric patients (below 18 years)
The pharmacokinetics of Tykerb in pediatric patients have not been established.

Geriatric patients (65 years or above)
Age does not appear to affect Tykerb pharmacokinetics, based on the analysis of individual study results. An examination of combined data, spanning a range of 18 to 82 years suggests no obvious effect.

Gender
Gender does not appear to affect Tykerb pharmacokinetics. An examination of combined data, including >300 females and >450 males, suggests no obvious difference.

Race/ethnicity
The available study data indicates no obvious distinction related to race/ethnicity.

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

Hepatic Impairment

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 Tykerb after a single oral 100 mg dose increased approx. 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 drug exposure. Dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on

therapy, Tykerb should be discontinued permanently (see Dosage regimen and administration and Warnings and precautions).

Pharmacogenomics

Polymorphic variations in drug-metabolizing enzymes, transporters, receptors, and other proteins that might affect Tykerb pharmacokinetics have not been explored.

The HLA alleles DQA1*02:01 and DRB1*07:01 were associated with hepatotoxicity in a genetic substudy of a monotherapy trial with Tykerb (see Warnings and precautions - Hepatotoxicity).

Clinical studies

The combination of Tykerb with capecitabine demonstrated superior efficacy versus capecitabine monotherapy in study EGF100151.

Data in two randomized studies in the metastatic settings (EGF111438 (CEREBREL) and EGF108919 (COMPLETE)) has shown that Tykerb combined with chemotherapy is less effective than trastuzumab combined with chemotherapy.

Tykerb was also studied in combination with letrozole and had superior efficacy versus letrozole alone in HER2-positive, hormone receptor-positive advanced or metastatic breast cancer patients.

See below for details.

Tykerb is not indicated in the adjuvant setting.

Combination treatment with Tykerb and capecitabine

Study EGF100151

The efficacy and safety of Tykerb in combination with capecitabine in breast cancer were evaluated in the randomized phase III study EGF100151. Patients eligible for enrollment had ErbB2 over-expressing (IHC 3+ or IHC 2+ and FISH positive), locally advanced or metastatic breast cancer, progressing after prior treatment including anthracyclines, taxanes and trastuzumab. LVEF was evaluated in all patients (using echocardiogram [Echo] or multi-gated acquisition scan [MUGA]) prior to initiation of treatment with Tykerb to ensure baseline LVEF was within the institutional normal limits. In clinical studies LVEF was monitored at approx. eight week intervals during treatment with Tykerb to ensure it did not fall below the institutional lower limit of normal (LLN). The majority of LVEF decreases (>60% of events) were observed during the first 9 weeks of treatment; however, limited data was available for long term exposure.

Patients were randomized to receive either 1250 mg Tykerb once daily (continuously) plus capecitabine 2,000 mg/m^2/day on Days 1 to 14 every 21 days, or to receive capecitabine alone at a dose of 2,500 mg/m^2/day on Days 1 to 14 every 21 days. The

endpoint was time to progression (TTP). TTP was defined as time from randomisation to tumour 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 oestrogen 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 1, Figure 1, and Figure 2.

Table 1 Study EGF100151 – Key efficacy results (TPP, ORR)

	Independent assessment*		**Investigator assessment**	
Efficacy outcome	**Tykerb plus capecitabine (N=198)**	**Capecitabine alone (N=201)**	**Tykerb plus capecitabine (N=198)**	**Capecitabine alone (N=201)**
TTP				
Progressed or died due to breast cancer	41%	51%	61%	63%
Median TTP (weeks)	27.1	18.6	23.9	18.3
HR, 95% CI (p-value)	0.57 (0.43, 0.77) 0.00013		0.72 (0.56, 0.92) 0.00762	
ORR, 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)

CI = confidence interval

ORR = Overall response rate

TTP = Time to progression.

*The time from last tumour 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

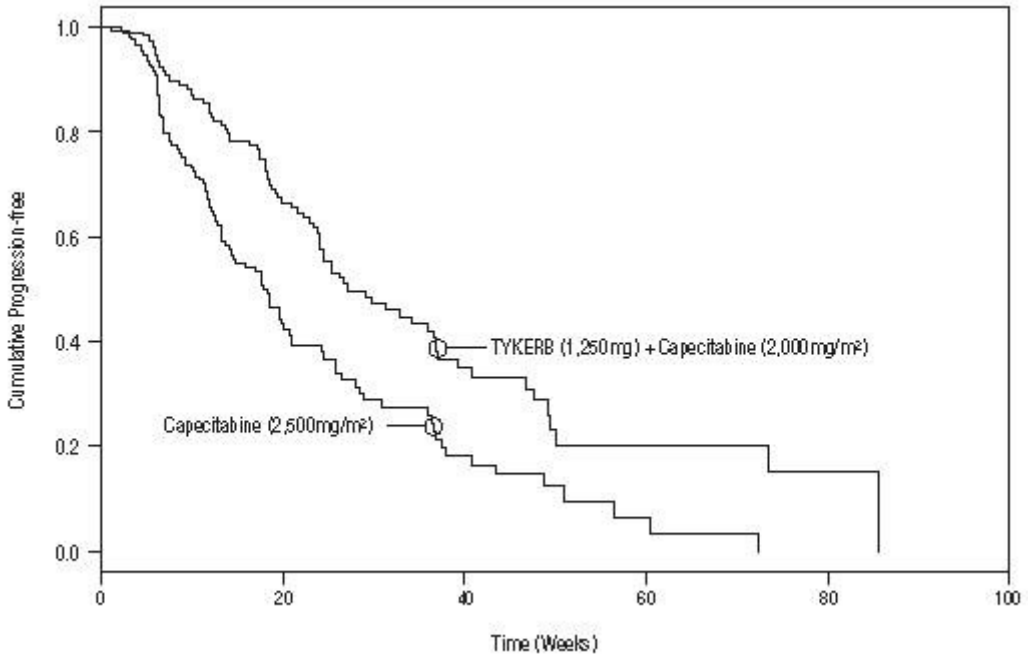
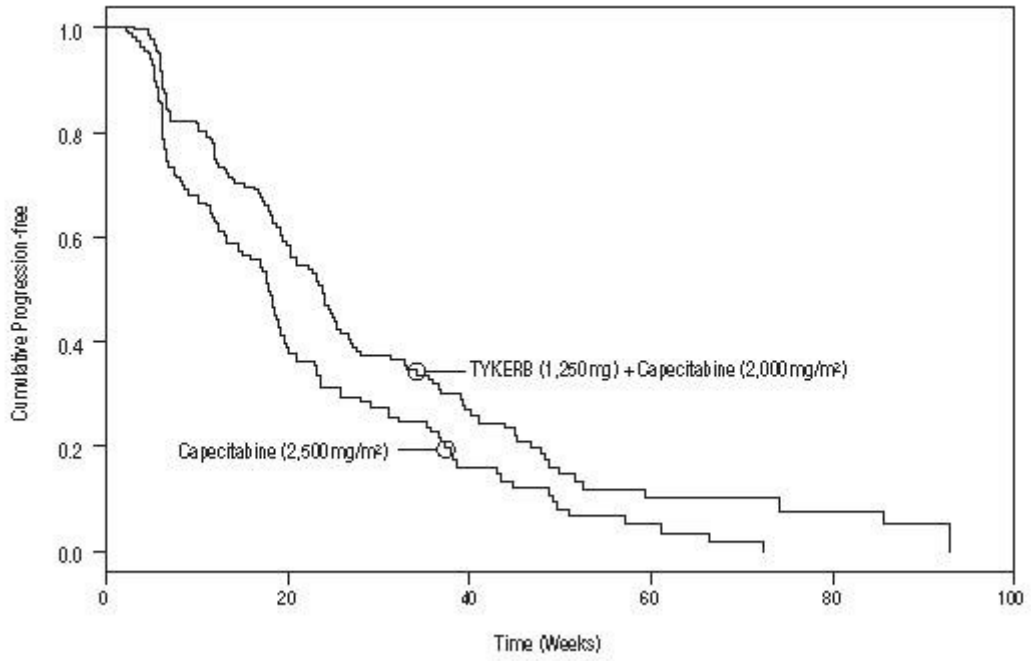


Figure 2 Kaplan-Meier Estimates for Investigator Assessment Time to Progression



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.

On the combination arm, there were 4 (2%) progressions in the central nervous system (CNS) versus the 13 (6%) progressions on the capecitabine monotherapy arm, as assessed by an independent review panel (see Clinical studies - Tykerb effect on CNS metastasis).

At the time enrollment was halted (3 April 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 to capecitabine monotherapy.

An analysis of survival data to 01 October 2008 is summarised in Table 2.

Table 2 Study EGF100151 - Key efficacy data (OS)

Efficacy outcome	Tykerb/Tyverb plus capecitabine (N=207)	Capecitabine alone (N=201)
OS		
Died	81%	86%
Median OS (weeks)	75.0	64.7
HR, 95% CI (p-value)	0.87 (0.71, 1.08) 0.210	

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. To isolate the treatment effect in the presence of cross-over, Cox regression analysis considering crossover as a time-dependent covariate and treatment effect was performed. The results from this analysis suggest a clinically relevant 20% reduction in risk of death, with a treatment effect hazard ratio of 0.80 (95% [CI]: 0.64, 0.99; p=0.043).

The QTc prolongation potential of Tykerb was assessed as part of an uncontrolled, open-label dose escalation study in advanced cancer patients. Eighty-one patients received daily doses of Tykerb 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 Tykerb 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-read evaluation of ECG. Analysis of the data suggested a relationship between Tykerb concentration and the QTc interval.

Study EGF111438 (CEREBEL)

A randomized phase III study (EGF111438) (N=540) compared the effect of Tykerb in combination with capecitabine to trastuzumab in combination with capecitabine on the incidence of the CNS as the site of first relapse in women with HER2 overexpressing metastatic breast cancer. Patients were randomized to either 1250 mg Tykerb once daily (continuously) plus capecitabine (2000 mg/m^2/day on days 1-14 every 21 days), or trastuzumab (loading dose of 8mg/kg followed by 6mg/kg infusions every 3 weeks) plus capecitabine (2500mg/m^2/day, on days 1-14, every 21

days). Randomisation was stratified by prior trastuzumab treatment and number of prior treatments for metastatic disease (none versus ≥1st line). The study was stopped when a pre-planned interim analysis (N=475) showed superior efficacy of the trastuzumab plus capecitabine arm and a low incidence of CNS events.

In the Tykerb plus capecitabine arm 8 patients (3.2%) experienced CNS as site of first progression versus 12 patients (4.8%) in the trastuzumab plus capecitabine arm (see Clinical Studies - Tykerb effect on CNS metastasis). The final analysis confirmed the superior efficacy of the trastuzumab plus capecitabine arm.

Table 3 Study EGF111438 – Key efficacy data (PFS, OS)

Efficacy outcome	Investigator-assessed PFS		OS	
	Tykerb + capecitabine	Trastuzumab + capecitabine	Tykerb + capecitabine	Trastuzumab + capecitabine
All patients				
N	271	269	271	269
Number (%) with event[1]	59%	50%	26%	22%
Kaplan-Meier estimate, months [a]				
Median (95% CI)	6.6 (5.7, 8.1)	8.0 (6.1, 8.9)	22.7 (19.5, -)	27.3 (23.7, -)
Stratified HR [b]				
HR (95% CI)	1.30 (1.04, 1.64)		1.34 (0.95, 1.90)	
p-value	0.021		0.095	
Patients who had received prior trastuzumab				
N	167	159	167	159
Number (%) with event[1]	103 (62)	86 (54)	43 (26)	38 (24)
Median (95% CI)	6.6 (5.7, 8.3)	6.1 (5.7, 8.0)	22.7 (20.1,-)	27.3 (22.5, 33.6)
HR (95% CI)	1.13 (0.85, 1.50)		1.18 (0.76, 1.83)	
Patients who had not received prior trastuzumab				
N	104	110	104	110
Number (%) with event[1]	57 (55)	48 (44)	27 (26)	20 (18)
Median (95% CI)	6.3 (5.6, 8.1)	10.9 (8.3, 15.0)	NE[2] (14.6, -)	NE[2] (21.6, -)
HR (95% CI)	1.70 (1.15, 2.50)		1.67 (0.94, 2.96)	

a. PFS was defined as the time from randomization to the earliest date of disease progression or death from any cause, or to the date of censor.

b. Pike estimate of the treatment hazard ratio, >1 indicates a higher risk for Tykerb/Tyverb plus capecitabine versus trastuzumab plus capecitabine.

1. PFS event is Progressed or died and OS event is died due to any cause.

2. NE= median was not reached.

Tykerb effect on CNS metastasis

In terms of objective responses, Tykerb monotherapy has demonstrated minimal activity in the treatment of established CNS metastases.

Tykerb is not recommended for the prevention of CNS metastases.

Combination treatment with Tykerb and letrozole

Study EGF30008

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

EGF30008 was a randomized, double-blind, placebo-controlled study in patients with hormone- receptor positive (HR+) locally advanced or metastatic breast cancer, who had not received prior systemic therapy for metastatic disease. 1286 patients were randomized to 2.5 mg letrozole once daily plus 1500 mg Tykerb once daily (N=642) or letrozole plus placebo. Randomisation was stratified by sites of disease and prior adjuvant anti-oestrogen therapy. ErbB2 receptor status was retrospectively determined by central laboratory testing. Of all patients randomized to treatment, 219 had tumours over-expressing the ErbB2 receptor, which was the pre-specified primary population for the analysis of efficacy. There were 952 ErbB2-negative patients and a total of 115 patients whose ErbB2 status was unconfirmed.

In the HER2-positive, hormone receptor-positive population, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus Tykerb than with letrozole plus placebo (see Table 4).

Table 4 Study EGF30008 - Key efficacy data (PFS)

	HER2-positive population	
	Tykerb 1500 mg/day + Letrozole 2.5 mg/day N=111	**Letrozole alone 2.5 mg/day N=108**
Median PFS, weeks (95% CI)	35.4 (24.1, 39.4)	13.0 (12.0, 23.7)
HR	0.71 (0.53, 0.96)	
p-value	0.019	

The benefit of Tykerb plus letrozole on PFS in the HER2-positive population was confirmed in a pre-planned Cox regression analysis (HR=0.65 (95% CI 0.47-0.89) p=0.008). In addition to a PFS benefit seen in this HER2 positive population, combination therapy of Tykerb and letrozole improved objective response rate (27.9% and 14.8% respectively) and clinical benefit rate (47.7% and 28.7% respectively) compared with letrozole treatment alone.

At the time of the final PFS analysis (with median follow-up of 2.64 years), the OS data were not mature and there was no significant difference between treatment groups in the HER2-positive population; this had not changed with additional follow-up (>7.5 years median follow-up time; Table 5).

Table 5 Study EGF30008 - Key efficacy data (OS in the HER2-positive population only)

	1500 mg / day Tykerb/Tyverb + 2.5 mg /day letrozole	2.5 mg /day letrozole + placebo
OS	N=111	N=108
Pre-planned OS analysis (conducted at the time of the final PFS analysis, 03 June 2008)		
Median follow-up (years)	2.64	2.64
Died	50 (45%)	54 (50%)
HR[a], 95% CI, P-value[b]	0.77 (0.52, 1.14) 0.185	
Final OS analysis (post-hoc analysis, 07 August 2013)		
Median Follow-up (yrs)	7.78	7.55
Died	86 (77%)	78 (72%)
Hazard ratio 95% CI	0.97 (0.7,1.3)	
P-value	0.842	

Median values from Kaplan-Meier analysis; HR and p-values from Cox regression models adjusting for important prognostic factors.

[a] Estimate of the treatment hazard ratio, where <1 indicates a lower risk with 2.5 mg letrozole + 1500 mg Tykerb versus 2.5 mg letrozole + placebo.

[b] p-value from Cox regression model, stratifying for site of disease and prior adjuvant therapy at screening.

Non-Clinical Safety Data

Safety Pharmacology

No neurological, respiratory or cardiovascular effects were identified in a panel of *in vitro* safety pharmacology studies or in *in vivo* animal studies with Tykerb.

Repeat dose toxicity

Tykerb was evaluated in repeat dose toxicity studies for up to 6 months in rats and up to 9 months in dogs. The principal treatment-related effects were inflammation and atrophy of the skin and adnexal structures, and degeneration and inflammation of the GI tract and accessory digestive organs (including liver), mammary gland and prostate. These effects were seen at ≥60 mg/kg/day in rats and ≥40 mg/kg/day in dogs. The No-Observed-Adverse-Effect Level (NOAEL) in male and female rats was 60 mg/kg/day and 10 mg/kg/day, respectively, with AUC estimates of 24.7 µg.h/mL and 25.1 µg.h/mL, respectively. The NOAEL in male and female dogs was 10 mg/kg/day with AUC estimates of 5.4 µg.h/mL and 8.2 µg.h/mL, respectively. Corresponding systemic exposures at these dose levels were 0.5 and 0.6-fold the human clinical exposure for male and female rats, respectively, and 0.1 and 0.2-fold the human clinical exposure for male and female dogs, respectively.

Indications

Tykerb, in combination with capecitabine, is indicated for the treatment of patients with advanced/metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline and, a

taxane, and who have progressed on prior trastuzumab therapy in the metastatic setting.

Tykerb, in combination with an aromatase inhibitor, is indicated for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2/neu (ErbB2) and for whom endocrine therapy is indicated. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor (see Clinical studies).

No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor chemotherapy in this patient population.

Contraindications

Tykerb is contraindicated in patients with hypersensitivity to any of the ingredients (see Adverse drug reactions).

Warnings and precautions

Cardiac toxicity:

Tykerb has been associated with decreases in left ventricular ejection fraction (LVEF) (see Adverse drug reactions). 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 it is within the institutionals normal limits. LVEF should be evaluated during treatment with Tykerb; this should be performed prior to the initiation of therapy and then approximately 8-12 week intervals to ensure that LVEF does not decline to an unacceptable level (see Dosage regimen and administration - dose delay and dose reduction - Cardiac events and Clinical studies).

In studies across the Tykerb clinical development program, cardiac events, including LVEF decreases were reported in approx. 1% of patients. Symptomatic LVEF decreases were observed in approx. 0.3% of patients who received Tykerb. However, when Tykerb was administered in combination with trastuzumab in the metastatic setting, the incidence of cardiac events including LVEF decreases was higher (7%) versus the Tykerb monotherapy arm (2%) in the pivotal study. The cardiac events observed in this study were comparable in nature and severity to those previously seen with Tykerb.

A concentration dependent QTc interval increase was observed in a dedicated placebo-controlled crossover study in patients with advanced solid tumors (see Clinical Pharmacology). Caution should be taken if Tykerb is administered to patients who have or may develop QTc interval prolongation.. This may include patients with hypokalemia or hypomagnesemia, congenital long QTc syndrome, patients taking anti-arrhythmic medicines or other medicinal products that cause QTc prolongation.

Hypokalemia, hypocalcaemia or hypomagnesemia should be corrected prior to Tykerb administration.

Tykerb should be administered with caution to patients who have or may develop prolongation of QTc (see Clinical Studies).

Interstitial lung disease and pneumonitis

Tykerb has been associated with interstitial lung disease and pneumonitis (see Adverse drug reactions). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (see Dosage regimen and administration).

Hepatotoxicity

Hepatotoxicity (ALT or AST >3 times the upper limit of normal (ULN) and total bilirubin >1.5 times the ULN) has been observed in clinical trials (<1% of patients) and post marketing experience. Hepatotoxicity may be severe and deaths have been reported, although the relationship to Tykerb is uncertain. 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 permanently (see Adverse drug reactions).

Patients carrying the HLA alleles DQA1*02:01 and DRB1*07:01 have an increased risk of Tykerb-associated hepatotoxicity. In a large, randomized clinical study of Tykerb monotherapy (EGF114471) (n=1,194), the overall risk of severe liver injury (ALT >5 times the ULN, 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.

If Tykerb is to be administered to patients with severe hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity on therapy, Tykerb should be discontinued permanently (see Dosage regimen and administration and Clinical pharmacology - Pharmacokinetics – Special populations).

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported with Tykerb (see Adverse drug reactions). Diarrhoea may be severe, and deaths have been reported. Diarrhoea generally occurs early during Tykerb treatment, with almost half of patients with diarrhoea first experiencing it within 6 days. This usually lasts 4 to 5 days. Tykerb-induced diarrhoea is usually low-grade, with severe diarrhoea of NCI CTCAE grades 3 and 4 occurring in <10% and <1% of patients, respectively. Early

identification and intervention is critical for the optimal diarrhoea management. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhoea with anti-diarrhoeals such as loperamide after the first unformed stool is recommended. Severe cases of diarrhoea may require oral or intravenous electrolytes and fluids, antibiotics such as fluoroquinolones (especially if diarrhoea persists beyond 24 hours, there is fever, or grade 3 or 4 neutropenia) or interruption or discontinuation of Tykerb (see Dosage regimen and administration - Dose delay and dose reduction - Diarrhoea).

Concomitant treatment with inhibitors or inducers of CYP3A4

Co-administration of CYP3A4 inhibitors or inducers requires caution due to the risk of increased or decreased exposure to Tykerb, respectively (see Interactions).

Severe cutaneous reactions

Severe cutaneous reactions have been reported with Tykerb. If erythema multiforme or life-threatening reactions such as Stevens-Johnson syndrome, or toxic epidermal necrolysis (progressive skin rash often with blisters or mucosal lesions) are suspected, treatment with Tykerb should be discontinued (see Dosage regimen and administration).

Patients with Renal Impairment

Refer to Pharmacokinetics-Renal Impairment.

Patients with Hepatic Impairment

Caution is warranted if Tykerb is prescribed to patients with moderate or severe hepatic impairment (Refer to Clinical Pharmacology - Pharmacokinetics-Hepatic Impairment).

Geriatric patients (65 years or above)

Refer to Dosage regimen and administration.

Pediatric patients (below 18 years)

Refer to Dosage regimen and administration.

Carcinogenicity and mutagenicity

In oral carcinogenicity studies with Tykerb, severe skin lesions were seen at the highest doses tested (150 and 300 mg/kg/day in male mice and 300 mg/kg/day in female mice, and 500 mg/kg/day in male rats and 300 mg/kg/day in female rats). Compared to humans given 1250 mg Tykerb and 2000 mg/m^2 capecitabine, these doses produced exposures based on AUC up to 1.7-fold higher in mice and male rats, and up to 12-fold

higher in female rats. There was no evidence of carcinogenicity in mice. In rats, an increase in the incidence of benign haemangioma of the mesenteric lymph node occurred in males given 120 mg/kg/day and female given 180 mg/kg/day, but was within the historical control background range. There was also an increase in renal infarcts and papillary necrosis in female rats at ≥60 mg/kg/day and 180 mg/kg/day, respectively (approx. 5.8 and 8.2 fold the clinical exposure in humans given 1250 mg Tykerb and 2000 mg/m^2 capecitabine, respectively. The relevance of these renal findings for humans is uncertain. Tykerb was not mutagenic in the bacterial reverse mutation assay (Ames test), or clastogenic in Chinese hamster ovary cells, or human lymphocytes *in vitro*, or an *in vivo* rat bone marrow chromosome aberration assay. Tykerb contains an impurity that was genotoxic *in vitro* and *in vivo*, however the levels of this impurity in the drug are considered acceptable given the proposed indication.

Reproductive toxicity

For data regarding the impact of Tykerb (lapatinib) on reproductive function, see Pregnancy, lactation, females and males of reproductive potential.

Infertility

Rat fertility was unaffected by Tykerb at doses (as free base) of up to 180 mg/kg/day (males) and 120 mg/kg/day (females), which correspond to exposures (AUC) that were approx. 2 and 8 times the human value with the recommended daily dose of 1250 mg, respectively. There was an increase in post-implantation loss in female fertility study at > 60 mg/kg/day (relative exposure approx. 4).

The effect of Tykerb on human fertility is unknown. There were no effects on rat gonadal function, mating or fertility at doses up to 120 mg/kg/day in females and 180 mg/kg/day in males (approx. 6.4 times and 2.6 times the expected human clinical exposure based on AUC following a 1250 mg dose of Tykerb plus capecitabine).

However, when female rats were given oral Tykerb during breeding and the first 6 days of gestation, a significant decrease in live fetuses was seen at 120 mg/kg/day and in fetal body weights at 60 mg/kg/day (approx. 6.4 times and 3.3 times the expected human clinical exposure, respectively based on AUC following a 1250 mg dose of Tykerb plus capecitabine).

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Animal data

In embryofetal development studies in rats and rabbits, pregnant animals received oral doses of 30, 60 and 120 mg/kg/day during organogenesis.

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 (approx. 6.4 times the human clinical exposure based on AUC following a 1250 mg dose of Tykerb plus capecitabine).

In rabbits, Tykerb was associated with maternal toxicity at 60 and 120 mg/kg/day (approx. 0.07 and 0.2 times the human clinical exposure respectively, based on AUC following a 1250 mg dose of Tykerb plus capecitabine) and abortions at 120 mg/kg/day. Maternal toxicity was associated with decreased foetal body weights, and minor skeletal variations.

In a pre- and postnatal development study, rats were given oral doses of 20, 60, and 120 mg/kg/day from gestation up to weaning. Doses of 60 and 120 mg/kg/day (approx. 3.3 and 6.4 times the human clinical exposure, respectively, based on AUC following a 1250 mg dose of Tykerb plus capecitabine) led to a decrease in F1 postnatal survival (91% and 34% of the pups died by the fourth day after birth, at 60 and 120 mg/kg/day, respectively) The highest no-effect dose for this study was 20 mg/kg/day (approx. equal to the human clinical exposure based on AUC).

Risk summary

Pregnant women should be advised of the potential risk to the fetus and Tykerb should be used during pregnancy only if the expected benefit for the patients justifies the potential risk to the foetus.

Tykerb was not teratogenic when studied in pregnant rats and rabbits but caused minor abnormalities at doses which were maternally toxic (see Animal data). If the drug is used during pregnancy or if the patient becomes pregnant while receiving the drug, the patient should be notified that Tykerb may cause harmful effects to the human foetus or neonate.

Lactation

Risk Summary

There are no data on the presence of Tykerb in human milk, or the effect of Tykerb on the breastfed infant, or on milk production. As many drugs are transferred into human milk and due to the potential for serious ADRs in breast- fed infants from Tykerb, it is advised that women should not breast-feed while receiving Tykerb and for at least 5 days after the last dose.

Females and males of reproductive potential

Contraception

Based on findings in animal studies, Tykerb can cause fetal harm. Females of reproductive potential should be advised to use effective contraception (methods that result in less than 1% pregnancy rates) while receiving Tykerb and for at least 5 days

after the last dose.

Interactions

Tykerb is predominantly metabolized by CYP3A (see Clinical pharmacology - Pharmacokinetics – Biotransformation/metabolism). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of Tykerb.

Interactions with CYP3A4-inhibitors

In healthy volunteers receiving ketoconazole, a CYP3A4 inhibitor, at 200 mg twice daily for 7 days, systemic exposure to Tykerb was increased approx. 3.6-fold, and half-life increased 1.7-fold.

Co-administration of Tykerb with known CYP3A4 inhibitors (e.g. erythromycin, telithromycin, ketoconazole, itraconazole, posaconazole, voriconazole, grapefruit juice, ritonavir, saquinavir, cisapride, verapamil, pimozide, nefazodone, cyclosporine) requires caution; clinical response and adverse events should be carefully monitored (see Warnings and precautions). If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a Tykerb dose reduction to 500 mg/day is predicted to adjust the 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 approx. one week should be allowed before the Tykerb dose is increased to the indicated dose.

Interactions with CYP3A4-inducer

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 Tykerb was decreased approx. 72%.

Co-administration of Tykerb with known CYP3A4 inducers (e.g. rifampin, rifabutin, phenytoin or carbamazepine or, Hypericum perforatum (St. John's wort) requires caution; clinical response and adverse events should be carefully monitored (see Warnings and precautions). If patients must be co-administered a strong CYP3A4 inducer, based on pharmacokinetic studies, Tykerb dose should be titrated gradually from 1250 mg/day up to 4500 mg/day or from 1500 mg/day to 5500 mg/day based on tolerability. This Tykerb dose is predicted to adjust the Tykerb 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 Tykerb dose should be reduced over approx. 2weeks to the indicated dose.

Drug that affect gastric pH

Pre-treatment with a proton pump inhibitor (esomeprazole) decreased Tykerb exposure by an average of 27% (range: 6% to 49%). This effect decreases with increasing age from approx. 40 to 60 years. Therefore, caution is required when

Tykerb is used in patients pre-treated with a proton pump inhibitor.

Effect of Tykerb on other drugs

Tykerb inhibits CYP3A4 *in vitro* at clinically relevant concentrations. Co-administration of Tykerb with oral midazolam resulted in an approx. 45% increase in midazolam AUC.. There was no clinically meaningful increase in AUC with IV midazolam. Caution is required when co-administering Tykerb with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (see Clinical pharmacology - Pharmacokinetics).

Tykerb inhibits CYP2C8 *in vitro* at clinically relevant concentrations. Caution is required when co-administering Tykerb with medications with narrow therapeutic windows that are substrates of CYP2C8 such as repaglinide (see Clinical pharmacology - Pharmacokinetics).

Combination therapy and non-fixed dose combination therapy

Co-administration of Tykerb with IV paclitaxel increased the paclitaxel exposure by 23%, due to Tykerb inhibition of CYP2C8 and/or P-glycoprotein (Pgp). An increase in the incidence and severity of diarrhoea and neutropenia has been observed with this combination in clinical studies. Caution is advised when Tykerb is co-administered with paclitaxel.

Co-administration of Tykerb with IV docetaxel did not significantly affect the AUC or C_{max} of either active substance. However, the occurrence of docetaxel-induced neutropenia increased.

Co-administration of Tykerb with irinotecan (when administered as part of the FOLFIRI regimen) resulted in an approx. 40% increase in the AUC of SN-38, the active metabolite of irinotecan. The precise mechanism of this interaction is unknown, but it is assumed to be due to inhibition of one or more transport proteins by Tykerb. Adverse reactions should be carefully monitored if Tykerb is co- administered with irinotecan, and a reduction in the dose of irinotecan should be considered.

Concomitant administration of Tykerb with capecitabine, letrozole or trastuzumab did not meaningfully alter the pharmacokinetics of these agents (or the metabolites of capecitabine) or Iapatinib (Tykerb).

Effect of Tykerb on transport proteins

Tykerb is a substrate for the transport proteins Pgp and Breast Cancer Resistance Protein (BCRP). Inhibitors and inducers of these proteins may therefore alter the exposure and/or distribution of Tykerb (see Clinical pharmacology - Pharmacokinetics).

Tykerb inhibits the transport protein Pgp *in vitro* at clinically relevant concentrations.

Co-administration of Tykerb with oral digoxin resulted in a 98% increase in digoxin AUC. Caution is required when co-administering Tykerb concurrently with medications with narrow therapeutic windows that are substrates of Pgp (e.g. quinidine).

Tykerb inhibits the transport proteins BCRP and OATP1B1 *in vitro*. The clinical relevance of this effect has not been evaluated. It cannot be excluded that Tykerb will affect the pharmacokinetics of substrates of BCRP (e.g. topotecan, quinidine) and OATP1B1 (e.g. rosuvastatin) (see Clinical pharmacology – Pharmacokinetics)

The bioavailability of Tykerb is affected by food (see Dosage regimen and administration and Clinical pharmacology - Pharmacokinetics).

Drug-food/drink interactions

The bioavailability of lapatinib is affected by food (see Dosage regimen and administration and Clinical pharmacology - Pharmacokinetics).

Grapefruit juice may inhibit CYP3A4 and Pgp in the gut wall, thereby it may increase the bioavailability of Tykerb and should therefore be avoided during treatment with Tykerb (see Interactions - Interactions with CYP3A4-inhibitors and Clinical Pharmacology - Biotransformation/Metabolism).

Adverse drug reactions

Summary of the safety profile

Clinical trial data

Safety of Tykerb has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in > 20,000 patients, including 198 patients in combination with capecitabine and 654 patients in combination with letrozole (see Clinical studies).

Tabulated summary of adverse drug reactions (ADRs) from clinical trials

ADRs from clinical trials are listed by MedDRA system organ class (SOC). Within each SOC, the ADRs are ranked by frequency, with the most frequent first. The corresponding frequency category for each ADRs is based on the following convention (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000).

ADRs with Tykerb Monotherapy

The following ADRs have been reported to be associated with Tykerb:

ADRs reported to be associated with Tykerb

ADR	Frequency category
Immune system disorders	
Hypersensitivity reactions including anaphylaxis[1]	Rare
Metabolism and nutrition disorders	
Anorexia	Very common
Cardiac disorders	
Decreased left ventricular ejection fraction[2]	Common
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease/pneumonitis	Uncommon
Gastrointestinal disorders	
Diarrhoea, which may lead to dehydration[3]	Very common
Nausea	Very common
Vomiting	Very common
Hepatobiliary disorders	
Hepatotoxicity[4]	Common
Hyperbilirubinaemia[5]	Very common
Skin and subcutaneous tissue disorders	
Rash[3] (including acneiform dermatitis)	Very common
Nail disorders including paronychia	Common
General disorders and administration site conditions	
Fatigue	Very common

[1] See Contraindications.

[2] LVEF decreases have been reported in approx. 1% of patients and were asymptomatic in >70% of cases. LVEF decreases resolved or improved in >70% of cases on discontinuation of Tykerb. Symptomatic LVEF decreases were observed in approx. 0.3% of patients on Tykerb. Observed adverse events included dyspnoea, cardiac failure and palpitations (see Dosage regime and administration - Dose delay and dose reduction - Cardiac events and Warnings and precautions).

[3] Diarrhoea and rash were generally low grade (most diarrhoea events were grade 1 or 2) and did not result in discontinuation of Tykerb. Diarrhoea responds well to proactive management (see Warnings and precautions). Rash was mostly transient (see Dosage regimen and administration - Dose delay and dose reduction - Other toxicities).

[4] ALT or AST >3 times ULN and total bilirubin >1.5 times ULN or serious hepatobiliary events associated with Tykerb or Hy's law cases.

[5] Elevated bilirubin may be due to Tykerb inhibition of hepatic uptake by Organic Anion Transporter Protein (OATPB1B1) or inhibition of excretion into bile by Pgp or BCRP.

ADRs with Tykerb in combination with capecitabine

In addition to the ADRs observed with Tykerb monotherapy, the following ADRs were reported to be associated with Tykerb in combination with capecitabine in study EGF100151 with a frequency difference > 5% versus capecitabine alone. These data are based on exposure to this combination in 198 patients.

ADRs occurring in EGF100151 with a frequency difference of > 5% versus capecitabine alone

ADR	**Frequency category**
Gastrointestinal disorders	
Dyspepsia	Very common
Skin and subcutaneous tissue disorders	
Dry skin	Very common

The following ADRs listed below were reported to be associated with Tykerb in

combination with capecitabine but were seen at a similar frequency in the capecitabine monotherapy arm.

Additional ADRs occurring in EGF100151 with a similar frequency for the combination versus capecitabine alone

ADR	Frequency category
Psychiatric disorders	
Insomnia	Very common
Nervous system disorders	
Headache	Common
Gastrointestinal disorders	
Stomatitis	Very common
Constipation	Very common
Abdominal pain	Very common
Skin and subcutaneous tissue disorders	
Palmar-plantar erythrodysaesthesia	Very common
Musculoskeletal and connective tissue disorders	
Pain in extremity	Very common
Back pain	Very common
General disorders and administrative site conditions	
Mucosal inflammation	Very common

Table 7 Most common study medication related adverse reactions (≥5%) in studies of Tykerb in combination with Capecitabine (EGF100151)

Preferred term	Tykerb 1250 mg + Capecitabine 2000 mg/m^2	Capecitabine (2500 mg/m^2)
	(N=164)	(N=152)
	%	%
Any related AEs	80	78
Diarrhoea	56	36
Palmar-plantar erythrodysaesthesia syndrome	44	47
Nausea	40	38
Rash	26	14
Vomiting	21	20
Stomatitis	14	10
Fatigue	13	23
Anorexia	13	18
Mucosal inflammation	10	11
Dry skin	10	5
Dyspepsia	7	2
Pain in extremity	7	6
Abdominal pain	5	12
Anaemia	5	5
Epistaxis	5	(<1)
Asthenia	4	8

Headache	4	5

Table 8 Selected hepatic laboratory abnormalities* observed during study EGF 100151

	Tykerb 1250 mg + Capecitabine 2000 mg/m^2			Capecitabine (2500 mg/m^2)		
	All Grades (%)	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades**	**Grade 3 (%)**	**Grade 4 (%)**
Total Bilirubin	45	3	0	30	2	0
AST	48	1	<1	42	2	0
ALT	36	2	0	31	2	0

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

An updated analysis inclusive of 75 subjects who were enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs. n=191 control arm) was performed. No difference in the safety profile was observed from that described previously. In this analysis 4% (7 subjects) treated with the combination arm and 1% (2 subjects) in the control arm experienced a decreased LVEF, although none were fatal and did not result in permanent discontinuation from the study.

Adverse reactions with Tykerb in combination with Letrozole

In addition to the ADRs observed with Tykerb monotherapy, the following ADRs were reported to be associated with Tykerb in combination with letrozole in study EGF30008 with a frequency difference of >5% versus letrozole alone. These data are based on exposure to this combination in 654 patients.

ADRs occurring with a frequency difference of >5% versus letrozole alone in study EGF30008

ADR	Frequency category
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Very common
Skin and subcutaneous tissue disorders	
Alopecia	Very common
Dry skin	Very common

Table 9 Most common study medication related adverse reactions (≥10%) for Tykerb in combination with letrozole (EGF30008)

Preferred term	Letrozole 2.5 mg + Tykerb 1500 mg	Letrozole 2.5 mg + Placebo
	N=654	N=624
	%	%
Any related AEs	84	55
Diarrhoea	53	13
Rash	38	9
Nausea	20	11
Dry skin	11	3
Fatigue	11	7
Alopecia	10	5
Nail disorder	10	<1
Pruritus	10	6

In the Tykerb plus letrozole treatment group, the most commonly observed study medication related serious adverse events were decreased left ventricular ejection fraction (LVEF) (2% of patients, compared to 1% for letrozole plus placebo). Other study medication related serious adverse events, including skin rash, hepatotoxicity and pneumonitis, were observed in <1% of patients. The most common adverse events leading to discontinuation of treatment in the Tykerb plus letrozole treatment group were diarrhoea (4%) and vomiting (2%).

Post Marketing Data

The following ADRs are from post-marketing experience with Tykerb via spontaneous case reports and literature cases. As 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. ADRs are listed according to MedDRA SOCs. Within each SOC, ADRs are presented in order of decreasing seriousness.

ADRs from spontaneous reports and literature (frequency not known)

ADR
Cardiac disorders
Ventricular arrhythmias/Torsades de Pointes
Electrocardiogram QT prolonged

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Skin Fissures[1]

[1]Frequency of skin fissures in pooled clinical trials data set was 4.9% (common)

Dosage regimen and administration

Dosage regimen and method of administration

Tykerb should only be initiated by a physician experienced in the administration of anti-cancer agents.

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 it does not fall below the institutional lower limit of normal (see Dosage regimen and administration - Dose delay and dose reduction — Cardiac events).

Tykerb should be taken at least 1 hour before, or at least 1 hour after food (see Interactions – Drug food interaction and Clinical pharmacology - Pharmacokinetics — Absorption). The recommended daily Tykerb dose should not be divided.

Missed doses should not be replaced and the dosing should resume with the next scheduled daily dose (see Overdosage).

The full prescribing information of the co-administered medicinal product should be consulted for details of its posology, and safety information.

General target population

Tykerb in combination with capecitabine

The recommended dose of Tykerb is 1250 mg (i.e. 5 tablets) once daily continuously when taken in combination with capecitabine.

The recommended dose of capecitabine is 2000 mg/m^2/day taken in 2 doses 12 hours apart on days 1-14 in a 21 day cycle (see Clinical studies). Capecitabine should be taken with food or within 30 minutes after food.

HER2 protein overexpression or gene amplification is necessary for the selection of patients for whom Tykerb therapy is appropriate. Evidence of a previous positive result for HER2 overexpression or gene amplification should be confirmed before initiating therapy with Tykerb. If are not available, repeat HER2 testing should be considered.

Assessment of HER2 overexpression and/or of HER2 gene amplification should be performed by laboratories with accreditation or demonstrated proficiency. HER2 overexpressing tumours are defined by a score of 3+ using an immunohistochemistry

(IHC)-based assessment, or IHC2+ and gene amplification or gene amplification alone.

Treatment with Tykerb should be continued until disease progression or unacceptable toxicity occurs.

Tykerb in combination with an aromatase inhibitor

The recommended dose of Tykerb is 1500 mg (i.e. 6 tablets) once daily continuously when taken in combination with an aromatase inhibitor.

When Tykerb is co-administered with the aromatase inhibitor letrozole, the recommended dose of letrozole is 2.5 mg once daily. If Tykerb is co-administered with an alternative aromatase inhibitor, please refer to the full prescribing information of the medicinal product for dosing details.

Dose delay and dose reduction (all indications)

Cardiac events (see Warnings and precautions)

Tykerb should be interrupted 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 institutionals LLN. Tykerb may be restarted at a lower dose (reduced from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day) after a minimum of 2 weeks and if LVEF recovers to normal and the patient is asymptomatic. Based on current data, the majority of LVEF decreases occur within the first 9 weeks of treatment, however, there is limited data on long term exposure.

Interstitial lung disease/pneumonitis (see Warnings and precautions and Adverse drug reactions)

Tykerb should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or higher.

Diarrhoea (see Warnings and precautions and Adverse drug reactions)

Tykerb should be interrupted in patients with diarrhoea 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 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day) when diarrhoea resolves to grade 1 or less. Tykerb should be permanently discontinued in patients with NCI CTCAE grade 4 diarrhoea.

Severe Cutaneous Reactions (see Warnings and precautions)

Tykerb should be discontinued in patients who experience severe progressive skin rash with blisters or mucosal lesions.

Other toxicities

Discontinuation or interruption of Tykerb may be considered if a patient develops toxicity greater than or equal to NCI CTCAE grade 2. Dosing can be restarted at the standard dose of 1250 mg/day or 1500 mg/day, if the toxicity improves to grade 1 or lower If the toxicity recurs, Tykerb should be restarted at a lower dose (reduced from 1250 mg/day to 1000 mg/day or from 1500 mg/day to 1250 mg/day).

Special population

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 under 2% of an administered dose (lapatinib and metabolites) is eliminated renally (see Clinical pharmacology -Pharmacokinetics — Special populations).

Hepatic impairment

Tykerb is metabolized in the liver. Moderate and severe hepatic impairment have been associated with 56% and 85% increases in systemic exposure, respectively. Administration of Tykerb to patients with hepatic impairment requires caution due to increased exposure. (see Warnings and precautions and Clinical pharmacology - Pharmacokinetics – Special populations).

Patients with severe hepatic impairment (Child-Pugh Class C) should have their Tykerb dose reduced. A dose reduction from 1250 mg/day to 750 mg/day or from 1500 mg/day to 1000 mg/day in patients with severe hepatic impairment is predicted to adjust the area under the curve (AUC) to the normal range. However, there is no clinical data with this dose adjustment in patients with severe hepatic impairment (see Warnings and precautions and Clinical pharmacology - Pharmacokinetics – Special populations).

Pediatric patients (below 18 years)

The safety and efficacy of Tykerb in pediatric patients has not been established.

Geriatric patients (65 years or above)

There are limited data on the use of Tykerb in patients aged 65 years and older. See Table 10.

Table 10 Number of geriatric patients

Clinical study	≥65 years	≥75 years
Tykerb plus capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
Tykerb/Tyverb plus letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent Tykerb/Tyverb (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

No age-based differences in the safety or efficacy of these regimens were observed. Other reported clinical experience has not identified differences in responses between the geriatric and younger patients. Greater sensitivity of geriatric patients cannot be ruled out.

Overdosage

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or HER2 tyrosine phosphorylation. The maximum oral dose of Tykerb in clinical trials was 1800 mg once daily.

Taking Tykerb more frequently than recommended 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 regimen and administration). Continuous ECG monitoring may be appropriate in cases of overdose.

Asymptomatic and symptomatic cases of overdose have been reported with Tykerb. Symptoms observed include known Tykerb associated events (see Adverse drug reactions) and in some cases sore scalp, sinus tachycardia (with otherwise normal ECG) and/or mucosal inflammation.

Tykerb is not significantly renally excreted and is highly bound to plasma proteins; therefore haemodialysis is not expected to enhance Tykerb elimination.

Further management should be as clinically indicated or as recommended by the national poisons center, where available.

Pharmaceutical information

Incompatibilities

No known incompatibilities

Special precautions for storage

Store up to 30°C.
Information might differ in some countries.
Tykerb must be kept out of the sight and reach of children.

Instructions for use and handling

No relevant information.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Pharmaceutical form

Film-coated tablets

Tykerb (Lapatinib ditosylate monohydrate) 250mg tablets are oval, biconvex, yellow film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

Active substance

Lapatinib ditosylate monohydrate.

The 250 mg film-coated tablet contains 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base.

TYKERB film-coated tablets are available in:

• High density polyethylene (HDPE) bottles with a child resistant polypropylene closure

• Blisters

Not all presentations are available in every country

Manufacturer

See folding box.

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Novartis Pharma AG, Basel, Switzerland