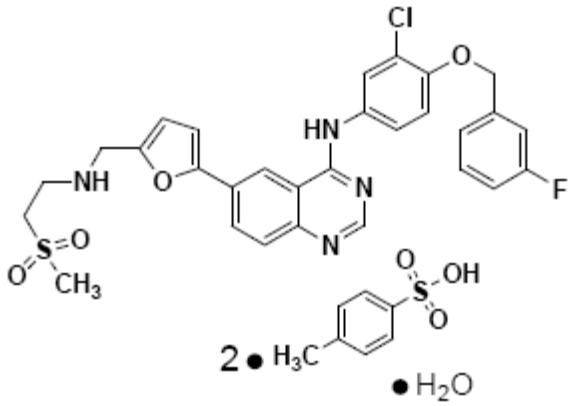
Attachment 1: Product information for AusPAR Tykerb GlaxoSmithKline Australia Pty Ltd PM-2011-00908-3-4 Final 12 November 2012. This Product Information was approved at the time this AusPAR was published.

TYKERB® PRODUCT INFORMATION
(Lapatinib as Ditosylate Monohydrate)
250 mg tablets

NAME OF THE MEDICINE

TYKERB® film-coated tablets contain lapatinib as ditosylate monohydrate 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.

The structural formula is:



Molecular formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$
Molecular weight: 943.48 (ditosylate monohydrate)
CAS number : 388082-78-8

DESCRIPTION

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.

TYKERB® 250 mg film-coated tablets contain microcrystalline cellulose, povidone K30, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, Polysorbate 80, Iron oxide red (CI77491) and Iron oxide yellow (CI77492).

PHARMACOLOGY

Lapatinib is a potent, reversible, and selective inhibitor of the intracellular tyrosine kinase domains of both ErbB1 (EGFR) and HER2 (ErbB2) receptors (estimated Ki^{app} values of 3nM and 13nM, respectively) with a slow off-rate from these receptors (half-life greater than or

equal to 300 minutes). This dissociation rate from ErbB1 (EGFR) was found to be slower for lapatinib than for erlotinib and gefitinib. Lapatinib 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 lapatinib were evaluated in trastuzumab-conditioned cell lines. Lapatinib 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 HER2 directed agents.

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

Pharmacokinetics

Absorption:

Absorption following oral administration of lapatinib 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 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. The absolute bioavailability of lapatinib has not been determined.

Daily dosing of 1500 mg lapatinib in combination with paclitaxel 175 mg/m^2 every three weeks produces steady state geometric mean (95% confidence interval) C_{max} values of 5.31 (3.54 to 7.97) µg/mL and AUC values of 64.5 (43.3 to 96.2) µg*hr/mL.

Systemic exposure to lapatinib is increased when administered with food *(See Dosage and Administration and 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 P-glycoprotein (ABCB1). Lapatinib has also been shown to inhibit P-glycoprotein (IC_{50} 2.3 µg/mL), BCRP (IC_{50} 0.015 µg/mL) and the hepatic uptake transporter OATP1B1(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. Limited inhibition of the OAT and OCT renal transporters was seen with 17µg/mL lapatinib.

Metabolism:

Lapatinib undergoes extensive metabolism, primarily by CYP3A4 and CYP3A5, with minor contributions from CYP2C19 and CYP2C8 to a variety of oxidated metabolites, none of which account for more than 14% of the dose recovered in the faeces or 10% of the lapatinib concentration in plasma. Furthermore, it is unlikely that any of these metabolites would contribute to the pharmacological activity of lapatinib.

Lapatinib significantly inhibited the metabolism of the substrates of the recombinant CYP enzymes, CYP3A4 and CYP2C8 in vitro at clinically relevant concentrations (~ 5 µM or 3 µg/mL). Lapatinib did not significantly inhibit the following enzymes in human liver microsomes: CYP2C9, CYP2C19 and CYP2D6 or UGT enzymes (in vitro IC_{50} values were greater than or equal to 6.9 µg/mL). Lapatinib was reported to inhibit the metabolism of substrates of recombinant CYP1A2, however it did not significantly inhibit CYP1A2 in human liver microsomes.

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.

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 approximately 72%.

Excretion:

The half-life of lapatinib measured after single doses increases with increasing dose (range 6 to 14 hours). However, daily dosing of lapatinib results in achievement of steady state within 6 to 7 days, indicating an effective half-life of 24 hours. The primary route of elimination for lapatinib and its metabolites is in faeces, with less than 2% of the dose (as lapatinib and metabolites) excreted in urine. Recovery of unchanged lapatinib in faeces accounts for a median 27% (range 3 to 67%) of an oral dose.

Special Populations:

Renal Impairment

Lapatinib 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 lapatinib given that less than 2% of an administered dose (as unchanged lapatinib and metabolites) is eliminated by the kidneys.

Hepatic Impairment

The pharmacokinetics of lapatinib 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 lapatinib in patients with hepatic impairment should be undertaken with caution due to increased exposure to the drug. A dose reduction is recommended for patients with severe pre-existing hepatic impairment. In patients who develop severe hepatotoxicity while on therapy, lapatinib should be discontinued and patients should not be retreated with lapatinib (*see Dosage and Administration and Precautions*).

CLINICAL TRIALS

Combination treatment with TYKERB and capecitabine

The efficacy and safety of TYKERB in combination with capecitabine in breast cancer was evaluated in a randomised, phase III trial (EGF100151). Patients eligible for enrolment had HER2 over-expressing, locally advanced or metastatic breast cancer, after prior treatment that included taxanes, anthracyclines and trastuzumab. LVEF was evaluated in all patients (using echocardiogram or MUGA) prior to initiation of treatment with TYKERB to ensure baseline LVEF was within the institutions normal limits.

In clinical trials, LVEF was monitored at approximately 8–week intervals during treatment with TYKERB to ensure it did not decline to below the institutions lower limit of normal. The majority of LVEF decreases (greater than 60%) were observed during the first nine weeks of treatment, however limited data was available for long term exposure.

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). The primary efficacy endpoint was time to tumour progression (TTP) as assessed by an independent review panel. TTP was defined as the time from randomisation to tumour progression or death related to breast cancer.

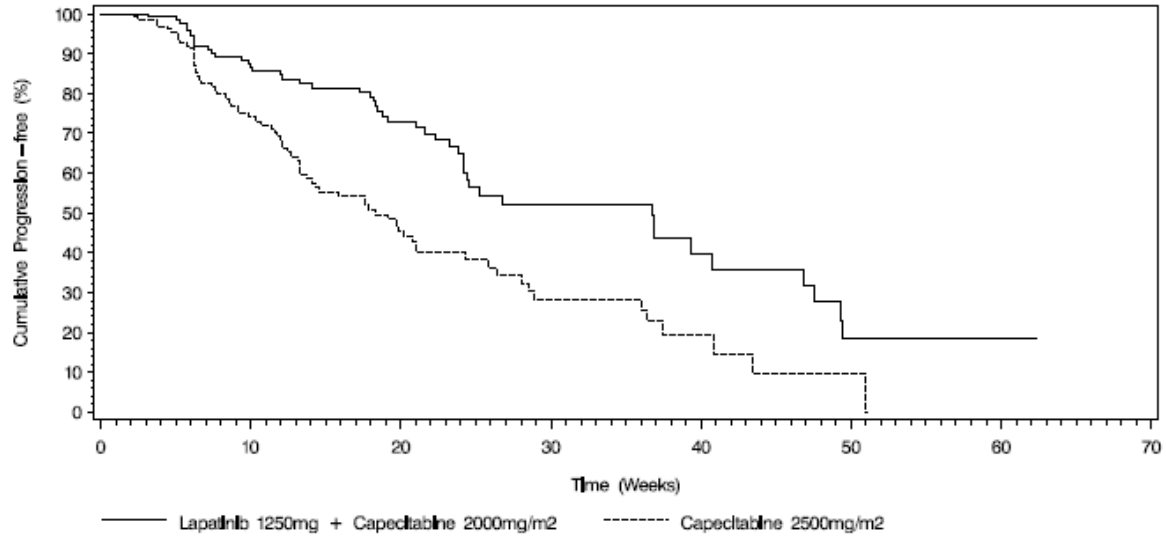
At the data cut-off date for the pre-specified interim analysis (November 15, 2005), 324 patients were enrolled (163 in the combination arm, 161 in the monotherapy arm). The efficacy results showed a statistically significant improvement in TTP (51% reduction in the hazard of disease progression) for patients receiving TYKERB plus capecitabine with a median TTP of 8.5 months in the combination arm versus 4.5 months in the monotherapy arm (p 0.00008). See Table 1.

Table 1: Efficacy results by Independent Review from EGF100151 clinical trial in locally advanced or metastatic breast cancer (Pre-specified Interim analysis)

Efficacy Outcome	TYKERB plus capecitabine (N=163)	Capecitabine alone (N=161)
Time to progression		
Progressed or died due to breast cancer	30%	45%
Median time to progression (months)	8.5	4.5
Hazard ratio, 95% CI (p value)	0.49 (0.34, 0.71) 0.00008	

The TTP data are represented graphically in Figure 1.

Figure 1: Kaplan-Meier Estimates of Time to Progression (TTP) by Independent review: TYKERB + capecitabine v capecitabine (Study EGF100151, pre-specified interim analysis)



Note: Four subjects who died due to causes other than breast cancer were censored.

Progression-free survival (PFS) is defined as time from randomisation until disease progression or death due to any cause. At the interim analysis, TYKERB, when given in combination with capecitabine significantly prolonged PFS compared to capecitabine alone (8.5 months v 4.1 months, p=0.000023).

The response rate (complete or partial response) independently assessed was 22% in the TYKERB plus capecitabine group compared with 14% in the capecitabine group (p = 0.091);

similar results were observed for the clinical benefit response rate (complete response + partial response + stable disease for at least 6 months), which was 27% vs 18% (p=0.069) in the combination versus the monotherapy arm, respectively.

At the time of interim analysis, the survival data were not sufficiently mature to detect a difference in overall survival between the treatment groups, 36 subjects (22%) in the TYKERB plus capecitabine group and 35 subjects (22%) in the capecitabine group had died. An exploratory analysis of patients with central nervous system (CNS) metastases showed four (2%) patients in the combination-therapy group had symptomatic CNS progression as part of their first progression event as compared to 11 (7%) patients in the monotherapy group (p=0.068).

An independent data monitoring committee (IDMC) initially reviewed the results of the interim analysis (which included data from 321 of the 324 patients), and recommended that further enrolment into the study be halted due to a statistically significant and clinically relevant increase in TTP for the combination of TYKERB and capecitabine over capecitabine alone, which crossed a pre-defined statistical stopping boundary for superiority. At the time enrolment was halted (April 03, 2006), a total of 399 patients had been randomised to study treatment.

A subsequent updated analysis was conducted with a data cut-off of April 03, 2006 when enrollment was halted. An additional 75 subjects had been enrolled into the study between the interim analysis clinical cut-off date and halting enrollment into the study (n=198 combination arm vs n= 201 control arm). This analysis revealed maintenance of a highly statistically significant improvement in TTP for subjects enrolled in the combination arm conferring a 43% reduction in hazard of disease progression (p=0.00013). The median TTP by independent review for the combination arm versus the control arm was 6.3 versus 4.3 months respectively.

The overall response rate, as assessed by an independent review panel was 23.7% for patients receiving lapatinib plus capecitabine and 13.9% for patients receiving capecitabine (p=0.017). Median duration of response was 7.4 months and 7 months respectively.

On the combination arm, there were 4 (2%) progressions in the central nervous system as compared with the 13 (6%) progressions on the capecitabine alone arm, as assessed by an independent review panel (p=0.045).

At the time enrolment was halted to EGF100151 (03 April 2006), 399 patients were randomised 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.

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

Table 2 Overall Survival data from Study EGF100151 (lapatinib / capecitabine)

	TYKERB plus capecitabine (N=207)	Capecitabine alone (N=201)
Overall Survival		
1. Died	81%	86%
2. Median overall survival (months)	17.30	14.9
3. Hazard ratio, 95% CI	0.87 (0.71, 1.08)	
4. (p value)	0.210	

CI = confidence interval

After the study was halted, 36 patients crossed over from capecitabine to TYKERB + 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 reduction in risk of death by 20%, with a treatment effect hazard ratio of 0.80 (95% confidence interval [CI]: 0.64, 0.99; p=0.043).

Combination treatment with TYKERB and paclitaxel

The efficacy and safety of TYKERB in combination with paclitaxel in breast cancer were evaluated in a randomised trial, EGF104535. Patients had histologically confirmed invasive breast cancer (Stage IV disease) that overexpressed HER2, and had not received prior therapy for metastatic disease.

Patients were randomly assigned to paclitaxel (80mg/m^2 intravenous on days 1, 8, and 15 of a 28 day schedule) and either TYKERB 1500mg/day or placebo once daily. Patients received a minimum of 6 cycles of TYKERB or placebo plus paclitaxel. After the 6 cycles of combination with paclitaxel were completed, patients continued on TYKERB or placebo until disease progression or an unacceptable toxicity occurred. The primary endpoint was overall survival (OS). Four hundred forty four (444) patients were enrolled in this study. Of the 222 patients who were on paclitaxel plus placebo, 149 patients (67%) with disease progression entered the open-label extension phase of the study and received TYKERB monotherapy. The median age was 50 years and 7% were older than 65 years. Eighty-six percent (86%) were Asian, 8% Hispanic, and 5% Caucasian. The overall survival data are summarised in Table 3 and represented graphically in Figure 2.

Table 3: Overall Survival Data

	TYKERB plus Paclitaxel (N = 222)	**Placebo plus Paclitaxel (N = 222)**
Died	54%	64%
Median overall survival (months)[1] (95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
Hazard ratio[2], 95% CI (Two-sided P value)	0.74 (0.58, 0.94) 0.0124	
Cox Regression[3] Hazard Ratio 95% CI (Two-sided P value)	0.64 (0.49, 0.82) 0.0005	

CI = confidence interval

[1] Kaplan-Meier estimates

[2] Pike estimator of hazard ratio

[3] Adjusted for hormonal status, metastatic disease sites, stage at initial diagnosis, ECOG Performance Status, number of metastatic sites, age and disease-free interval.

A summary of other key efficacy endpoints are provided in Table 4.

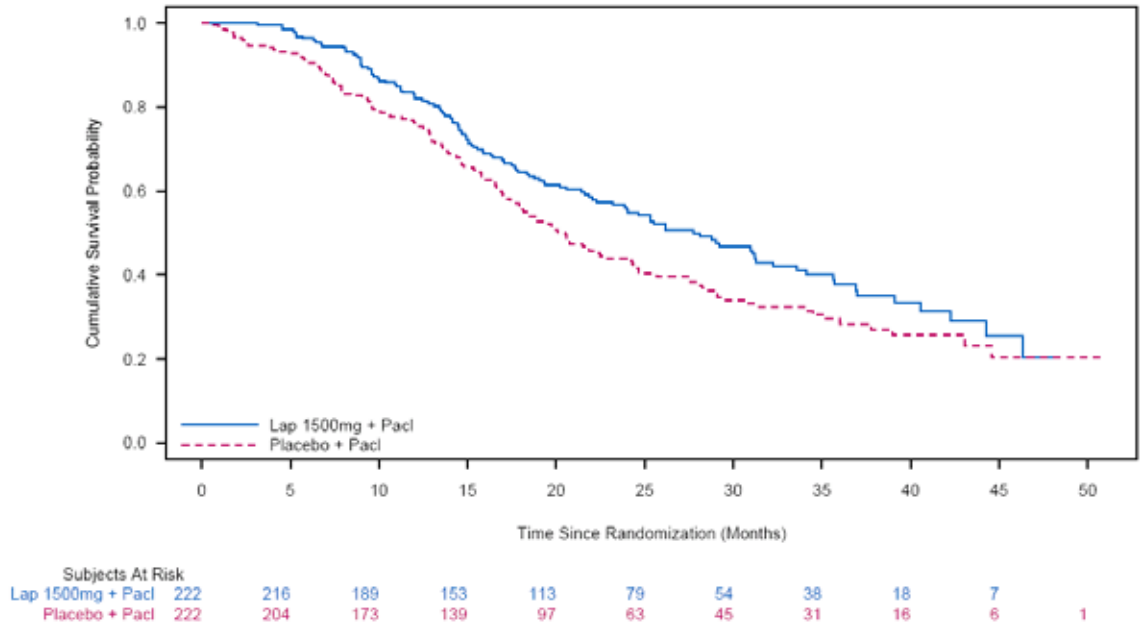
Table 4: Efficacy Data

	TYKERB plus Paclitaxel (N = 222)	**Placebo plus Paclitaxel (N = 222)**
Median PFS[1], months (95% CI)	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
Hazard Ratio (95% CI) P value	0.52 (0.42, 0.64) <0.0001	
Response Rate (%) (95% CI)	69 (62.9, 75.4)	50 (42.8, 56.3)
Duration of Response, months (95% CI)	9.3 (7.7, 10.7)	5.8 (5.6, 7.4)

PFS = progression-free survival; CI = confidence interval.

[1] Kaplan-Meier estimate.

Figure 2 Kaplan-Meier Estimates of Overall Survival (ITT Population)



Another randomised, double-blind, controlled study evaluated TYKERB and paclitaxel as first-line therapy for metastatic breast cancer in patients with negative or untested HER2 status and previously untreated in the metastatic setting (EGF30001). Patients (N= 579) were randomly assigned 1:1 to paclitaxel (175mg/m^2 intravenously over 3 hours on day 1, every 3 weeks) and either TYKERB 1500mg/day or placebo once daily. Sixty-four percent (64%) were Caucasian, 18% Hispanic, and 11% Asian. There were 91 patients (16%) with HER2 positive disease.

The primary endpoint was time-to-progression (TTP); secondary endpoints included progression free survival (PFS), tumour response rate (RR), clinical benefit rate (CBR), overall survival (OS) and safety. No significant differences in TTP or PFS were observed between treatment arms in the unselected ITT population. In the HER2 positive subgroup, statistically significant and clinically relevant benefit was observed in TTP and PFS in favour of the TYKERB plus paclitaxel group. The median TTP in the HER2 positive subgroup was 35.1 weeks in the TYKERB plus paclitaxel group compared to 23.1 weeks in the paclitaxel plus placebo group (hazard ratio of 0.57; 95% CI: 0.34, 0.93; p = 0.011). The median PFS in the HER2 positive subgroup was 34.4 weeks (95% CI: 32.1, 41.6) in the TYKERB plus paclitaxel combination compared to 22.6 weeks (95% CI: 20.1, 32.9) in the paclitaxel plus placebo group (hazard ratio of 0.56; 95% CI: 0.34, 0.90; p = 0.007). The overall survival analysis of the ITT population and HER2 positive subgroup are presented in Table 5.

Table 5: Overall Survival data from Study EGF30001 (TYKERB/paclitaxel 175mg/m^2)

	TYKERB plus paclitaxel	**Paclitaxel alone**
Overall Survival HER2+ Population)	**(N=52)**	**(N=39)**
Died	71%	74%
Median overall survival (months) (95% CI)	24.3 (17.7, 31.3)	19.2 (11.7, 29.7)
Hazard ratio, 95% CI (p value)	0.77 (0.5, 1.3) 0.281	

CI = confidence interval

Data from a pre-planned interim analysis are available on the efficacy and safety of lapatinib+taxane relative to trastuzumab+taxane. A randomized Phase III study (EGF108919) comparing the activity of lapatinib plus taxane followed by lapatinib alone versus trastuzumab plus taxane followed by trastuzumab as first-line therapy for women with HER2+ metastatic breast cancer was stopped early due to superior efficacy of the trastuzumab+taxane in terms of progression-free survival. Interim safety data also showed an increase in the frequency of specific Grade 3-4 adverse events, including diarrhoea, rash, fatigue and febrile neutropenia, in the study arm receiving lapatinib compared with the study arm receiving trastuzumab. At the time of the interim analysis, overall survival data were not mature to make any definitive conclusions.

Combination treatment with TYKERB and letrozole

TYKERB has been studied in combination with the aromatase inhibitor 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 Phase III, randomised, double-blind, controlled trial in patients with hormone receptor-positive locally advanced or metastatic breast cancer (MBC), who had not received prior systemic therapy for their metastatic disease. 1286 patients were randomised to letrozole 2.5 mg once daily plus TYKERB 1500 mg once daily or letrozole 2.5 mg with placebo. Randomisation was stratified by sites of disease and prior adjuvant anti-oestrogen therapy. HER2 receptor status was retrospectively determined by central laboratory testing.

Of all patients randomised to treatment, 219 patients had tumours over-expressing the HER2 receptor (the 'HER2-positive population'), which was the pre-specified primary population for the analysis of efficacy. There were 952 HER2 negative patients and a total of 115 patients whose HER2 status was unconfirmed.

In the HER2-positive population, investigator-determined progression-free survival (PFS) was significantly greater with letrozole plus TYKERB compared with letrozole plus placebo (see Table 6).

Table 6 Progression Free and Overall Survival data from Study EGF30008 (TYKERB / letrozole)

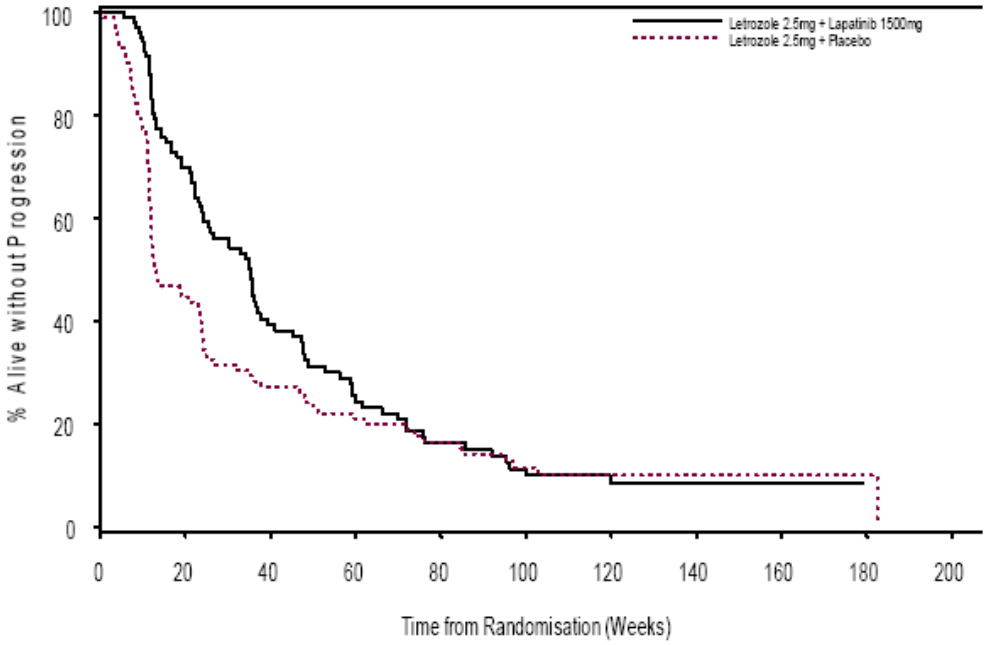
	Primary endpoint		**Secondary endpoints**			
	HER2-Positive Population		**Intent-to-Treat Population**		**HER2-Negative Population**	
	N = 111	**N = 108**	**N = 642**	**N = 644**	**N = 478**	**N = 474**
	TYKERB 1500 mg / day + Letrozole 2.5 mg / day	**Letrozole 2.5 mg / day + placebo**	**TYKERB 1500 mg / day + Letrozole 2.5 mg / day**	**Letrozole 2.5 mg / day + placebo**	**TYKERB 1500 mg / day + Letrozole 2.5 mg / day**	**Letrozole 2.5 mg / day + placebo**
Median PFS, months (95% CI)	8.2 (5.6, 9.1)	3.0 (2.8, 5.5)	11.9 (10.9, 13.7)	10.8 (8.5, 11.7)	13.7 (11.2, 16.0)	13.4 (11.0, 14.3)
Hazard Ratio	0.71 (0.53, 0.96)		0.86 (0.76, 0.98)		0.90 (0.77, 1.05)	
P-value	0.019		0.026		0.188	
Median OS, months (95% CI)	33.3 (22.0 – NE)	32.3 (21.2 – 36.7)	39.4 (36.3, 45.1)	40.5 (35.9, 43.6)	40.1 (37.1, NE)	41.3 (38.8, NE)
Hazard Ratio	0.74 (0.5, 1.1)		1.01 (0.8, 1.2)		1.15 (0.9, 1.4)	
P-value	0.113		0.915		0.193	

CI= confidence interval

NE= Non-evaluable

The PFS data in the HER2-positive population is represented graphically in Figure 3.

Figure 3: Kaplan-Meier Estimates for Investigator-Evaluated PFS (Study EGF30008, HER2 +ve Population)



The benefit of TYKERB + 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 the HER2+ patient population, combination therapy of TYKERB and letrozole was associated with a significant improvement in objective response rate (27.9 % and 14.8 % respectively) (p=0.021) compared with treatment with letrozole plus placebo. Although not yet mature, a trend towards a survival benefit was noted for the TYKERB/letrozole combination, HR= 0.74 (95 % CI 0.50, 1.1) p=0.113 (see Table 6).

In the Intent-to-Treat (ITT) population, investigator-determined PFS was greater between the two treatment arms (see Table 6). Although statistically significant, the difference was not considered clinically relevant.

In the HER2-negative population (n=952), the Kaplan-Meier analyses for PFS did not show a significant difference between the two treatment arms (see Table 6).

INDICATIONS

TYKERB, in combination with an aromatase inhibitor, is indicated for the treatment of post-menopausal women with hormone receptor-positive metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom hormonal therapy is indicated.

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, a taxane and trastuzumab.

TYKERB, in combination with paclitaxel, is indicated for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and for whom trastuzumab is not appropriate *(see Clinical Trials)*.

CONTRAINDICATIONS

TYKERB is contraindicated in patients with hypersensitivity to any of the ingredients *(see Description and Adverse Events)*.

PRECAUTIONS

TYKERB has been associated with reports of decreases in left ventricular ejection fraction [LVEF] (*see Adverse Events*). Caution should be taken if TYKERB is to be administered to patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with TYKERB to ensure that the patient has a baseline LVEF that is within the institutions 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 and Administration — Dose delay and dose reduction — Cardiac events and Clinical Trials*).

TYKERB has been associated with reports of interstitial lung disease and pneumonitis (*see Adverse Events*). Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis (*see Dosage and Administration*).

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 postmarketing experience. The 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 and patients should not be retreated with TYKERB (*see Adverse Events*).

Diarrhoea, including severe diarrhoea, has been reported with TYKERB treatment (*see Adverse Events*). Early identification and intervention is critical for the optimal management of diarrhoea. Patients should be instructed to report any change in bowel patterns immediately. Prompt treatment of diarrhoea with anti-diarrhoeal agents (such as

loperamide) after the first unformed stool is recommended. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of TYKERB therapy (*see Dosage and Administration — Dose delay and dose reduction — Other toxicities*).

Neutropenia has been reported with TYKERB administered in combination with paclitaxel (*see Adverse Events and Interactions*). Complete blood counts should be monitored regularly during treatment with this combination. *(see Dosage and Administration – Dose Delay and dose reduction – administration with paclitaxel).*

Concomitant treatment with inhibitors or inducers of CYP3A4 should proceed with caution due to risk of increased or decreased exposure to TYKERB, respectively (*see Interactions*).

Limited data suggest that TYKERB in combination with paclitaxel is less effective and not as tolerable as trastuzumab in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer whose tumours overexpress HER2 (ErbB2). Therefore lapatinib-paclitaxel should be used in patients for whom trastuzumab is not appropriate *(see Clinical Trials).*

Patients with renal impairment:
Refer to Pharmacokinetics.

Patients with Hepatic Impairment:
If TYKERB is to be administered to patients with severe pre-existing hepatic impairment, dose reduction is recommended. In patients who develop severe hepatotoxicity while on therapy, TYKERB should be discontinued and patients should not be retreated with TYKERB (*see Dosage and Administration and Pharmacokinetics – Hepatic Impairment*).

Effects on fertility:
Rat fertility was unaffected by lapatinib 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 approximately 2 and 8 times the expected clinical exposure, respectively. There was an increase in post implantation loss in the female fertility study at > 60 mg/kg/day (relative exposure approximately 4). The effect on human fertility is unknown.

Use in Pregnancy (Category C)
Lapatinib was studied in pregnant rats and rabbits given oral doses of 30, 60 and 120 mg/kg/day. There were no treatment-related malformations, however alterations (left-sided umbilical artery, cervical rib) were observed in rats in the presence of maternal toxicity at 120 mg/kg/day (approximately 6 times the clinical exposure based on AUC). An increased number of early post implantation losses were also seen in rats treated at 120 mg/kg/day,

while precocious ossification was observed in rats in all treatment groups, independent of maternal toxicity or foetal body weight changes.

In rabbits, an increased incidence of fetuses and litters with minor skeletal variations was seen at ≥ 60 mg/kg/day, in the presence of decreased maternal body weight and clinical signs. Abortions were seen in doses treated at 120 mg/kg/day. Lapatinib exposures at 60 and 120 mg/kg/day in the rabbit study were approximately 10 and 20% respectively, the clinical exposure (based on AUC).

In the pre- and postnatal development study, a marked decrease in pup survival occurred between birth and postnatal day 21 at doses of ≥ 60 mg/kg/day (approximately 3 times the expected clinical exposure based on AUC). The highest no-effect dose for this study was 20 mg/kg/day, similar to the clinical exposure.

There are no adequate and well-controlled studies of TYKERB in pregnant women. The effect of TYKERB on human pregnancy is unknown. TYKERB should not be used in pregnancy. Women of childbearing potential must be advised to use adequate contraception and avoid becoming pregnant while receiving treatment with TYKERB. 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 fetus or neonate.

Use in Lactation
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 breast-feeding infants from TYKERB, women who are receiving therapy with TYKERB should not breastfeed.

Paediatric Use
Refer to Dosage and Administration.

Use in Elderly:
Refer to Dosage and Administration

Genotoxicity:
Lapatinib 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. Lapatinib 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.

Carcinogenicity:

In oral carcinogenicity studies with lapatinib, severe skin lesions were seen at the highest doses tested which produced exposures based on AUC up to 2-fold in mice and male rats, and up to 8-fold in female rats, the anticipated clinical AUC. There was no evidence of carcinogenicity in mice. In rats, the incidence of benign haemangioma of the mesenteric lymph nodes was higher in some groups than in concurrent controls, but was within background range. There was also an increase in renal infarcts and papillary necrosis in female rats at exposures 5 and 8-fold the anticipated clinical AUC. The relevance of these findings for humans is uncertain.

INTERACTIONS WITH OTHER MEDICINES

TYKERB is predominantly metabolised by CYP3A (*see Pharmacokinetics*). Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of TYKERB. Coadministration of TYKERB with known inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or grapefruit juice) should proceed with caution and clinical response and adverse events should be carefully monitored (*see Precautions*). If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of TYKERB is predicted to adjust the TYKERB AUC to the range observed without inhibitors and should be considered. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the TYKERB dose is adjusted upward to the indicated dose.

Coadministration of TYKERB with known inducers of CYP3A4 (e.g., rifampicin, carbamazepine, or phenytoin) should proceed with caution and clinical response and adverse events should be carefully monitored (*see Precautions*). If patients must be coadministered a strong CYP3A4 inducer, the dose of TYKERB should be titrated gradually, based on tolerability. 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 approximately 2 weeks to the indicated dose.

The solubility of TYKERB is pH-dependent. Concomitant treatment with substances that increase gastric pH should be avoided since TYKERB solubility and absorption may decrease. 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 approximately 40 to 60 years. Therefore, caution should be used when TYKERB is used in patients pre-treated with a proton pump inhibitor.

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 when dosing TYKERB concurrently

with orally administered medications with narrow therapeutic windows that are substrates of CYP3A4 (*see Pharmacokinetics*).

TYKERB inhibits CYP2C8 at clinically relevant concentrations. Caution should be exercised (see Pharmacokinetics) when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8 (*see Pharmacokinetics*).

Coadministration of lapatinib with intravenous paclitaxel increased the exposure of paclitaxel by 23%, due to lapatinib 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 trials. Caution is advised when lapatinib is coadministered with paclitaxel.

TYKERB is a substrate for the transport proteins P-glycoprotein and BCRP (Breast Cancer Resistance Protein). Inhibitors and inducers of these proteins may alter the exposure and/or distribution of lapatinib.

TYKERB inhibits the transport protein P-glycoprotein in vitro at clinically relevant concentrations. Coadministration of lapatinib with orally administered digoxin resulted in an approximate 98% increase in the AUC of digoxin. Caution should be exercised when dosing lapatinib concurrently with medications with narrow therapeutic windows that are substrates of Pgp.

Lapatinib inhibits the transport proteins BCRP and OATP1B1 in vitro. The clinical relevance of this effect has not been evaluated. It cannot be excluded that lapatinib will affect the pharmacokinetics of substrates of BCRP (e.g. topotecan) and OATP1B1 (e.g. rosuvastatin).

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

The bioavailability of TYKERB is affected by food (*see Dosage and Administration and Pharmacokinetics*).

Driving or operating machinery

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 TYKERB, although in clinical studies, fatigue is a very common adverse event associated with TYKERB treatment. If patients experience fatigue, weakness or tiredness, they should be advised not to drive or operate machinery (see *Adverse Events)*.

ADVERSE EFFECTS:

Safety of TYKERB has been evaluated as monotherapy or in combination with other chemotherapies for various cancers in more than 19,000 patients, including 198 patients who received TYKERB in combination with capecitabine, 222 patients who received TYKERB in combination with paclitaxel (80mg/m^2 weekly), 293 patients who received TYKERB in combination with paclitaxel (175mg/m^2 every 3 weeks), and 654 patients who received TYKERB in combination with letrozole (*see Clinical Trial*s).

The following convention has been utilised for the classification of frequency: Very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000).

TYKERB monotherapy

The following adverse reactions have been reported to be associated with TYKERB:

Metabolism and nutrition disorders	
Very common	Anorexia.
Cardiac disorders	
Common	Decreased left ventricular ejection fraction[1] (*see Dosage and Administration — dose delay and dose reduction — Cardiac events and Precautions*).
[1]Left ventricular ejection fraction (LVEF) decreases have been reported in approximately 1% of patients and were asymptomatic in more than 70% of cases. LVEF decreases resolved or improved in more than 60% of cases on discontinuation of treatment with TYKERB. Symptomatic LVEF decreases were observed in approximately 0.3% of patients who received TYKERB. Observed symptoms included dyspnoea, cardiac failure and palpitations.	
Respiratory, thoracic and mediastinal disorders:	
Uncommon	Interstitial lung disease / pneumonitis (*see Dosage and Administration and Precautions*)
Gastrointestinal disorders	
Very common	Diarrhoea[2], which may lead to dehydration [3](*see Dosage and Administration — dose delay and dose reduction — Other toxicities and Precautions*). Nausea. Vomiting.
[3]Most events of diarrhoea were grade 1 or 2.	
Hepatobiliary disorders	

Very common	Hyperbilirubinaemia[4].
Common	Hepatotoxicity.
[4]Elevated bilirubin may be due to TYKERB inhibition of hepatic uptake by OATP1B1 or inhibition of excretion into bile by Pgp or BCRP.	
Skin and subcutaneous tissue disorders	
Very common	Rash[2] (including dermatitis acneform) (*see Dosage and Administration — dose delay and dose reduction — Other toxicities*).
Common	Nail disorders including paronychia
Immune System Disorders	
Rare	Hypersensitivity reactions including anaphylaxis (*see Contraindications)*
General disorders and administration site conditions	
Very common	Fatigue.

[2]Diarrhoea and rash were generally low grade and did not result in discontinuation of treatment with TYKERB. Diarrhoea responds well to proactive management (*see Precautions*). Rash was transient in the majority of cases.

TYKERB in combination with capecitabine

In addition to the adverse reactions observed with TYKERB monotherapy, the following adverse reactions have been reported to be associated with TYKERB in combination with capecitabine with a frequency difference of greater than 5% compared to capecitabine alone. These data are based on exposure to this combination in 198 patients.

Gastrointestinal disorders	
Very common	Dyspepsia.
Skin and subcutaneous tissue disorders	
Very common	Dry skin.

The following adverse reactions were reported to be associated with TYKERB in combination with capecitabine but were seen at a similar frequency in the capecitabine alone arm.

Gastrointestinal disorders	
Very common	Stomatitis, constipation, abdominal pain.
Skin and subcutaneous tissue disorders	
Very common	Palmar-plantar erythrodysaesthesia.
General disorders and administrative site conditions	
Very common	Mucosal inflammation.
Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity, back pain.
Nervous system disorders	

Common	Headache.
Psychiatric disorders	
Very common	Insomnia.

Table 7 Most common study medication related adverse reactions (³ 5%) in studies of TYKERB in combination with Capecitabine (EGF100151 03 April 2006 Cut Off)

Preferred term	Lapatinib 1250mg + Capecitabine 2000mg/m^2	Capecitabine (2500 mg/m^2)
	(N = 198)	(N=191)
	%	%
Any related AEs	87	82
Diarrhoea	60	37
Palmar-plantar erythrodysaesthesia syndrome	49	49
Nausea	40	39
Rash	25	12
Vomiting	20	17
Stomatitis	13	9
Fatigue	18	21
Anorexia	11	18
Mucosal inflammation	14	11
Dry skin	9	6
Dyspepsia	8	2
Pain in extremity	6	5
Abdominal pain	6	12
Anaemia	5	5
Epistaxis	7	(<1)
Asthenia	7	9
Headache	4	5
Neutropenia	3	6
Nail Disorder	5	2
Peripheral sensory neuropathy	1	5

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

	Lapatinib 1250mg + Capecitabine 2000mg/m^2			**Capecitabine (2500 mg/m^2)**		
	All Grades	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades**	**Grade 3 (%)**	**Grade 4 (%)**
Total Bilirubin	45	4	0	30	3	0
AST	49	2	<1	43	2	0

ALT	37	2	0	33	2	0

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

TYKERB in combination with paclitaxel

The following additional adverse reactions have been reported to be associated with TYKERB in combination with paclitaxel (80 mg/m^2 weekly) with a frequency of greater than 5% compared to paclitaxel alone. These data are based on exposure to this combination in 222 patients.

Blood and lymphatic system disorders	
Very common	Neutropenia (*see Precautions*). Leukopenia. Anaemia.
Nervous system disorders	
Very common	Neuropathy peripheral.*
Musculoskeletal and connective tissue disorders	
Very common	Myalgia.*

*additional adverse reactions report in 293 patients on TYKERB in combination with paclitaxel (175mg/m^2 every 3 weeks) with a frequency difference of greater than 5% compared to paclitaxel alone.

Table 9. Adverse Reactions Occurring in ³ 10% of Patients in a study of TYKERB in combination with paclitaxel (EGF 104535)

	TYKERB 1,500 mg/day + Paclitaxel 80 mg/m² IV weekly (N = 222)			Paclitaxel 80 mg/m² IV weekly (N = 221)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Blood and Lymphatic System Disorder						
Neutropenia	77	35	16	47	15	5
Leukopenia	53	23	3	33	8	<1
Anaemia	23	4	0	10	1	0
Skin and subcutaneous tissue disorders						
Rash	59	4	<1	24	0	0
Nail disorder	11	0	0	1	0	0
Gastrointestinal disorders						
Diarrhoea	77	20	0	29	<1	<1
Nausea	30	<1	0	19	0	0
Vomiting	22	2	0	12	1	0
General disorders and administrative site conditions						
Fatigue	22	2	0	16	<1	0
Investigations						
ALT increased	11	2	0	8	<1	0
Haemoglobin decreased	10	3	0	2	<1	0
Metabolism and nutrition disorders						
Decreased appetite	32	<1	0	19	0	0
Musculoskeletal and connective tissue disorders						
Myalgia	14	<1	0	10	0	0
Respiratory, thoracic, and mediastinal disorders						
Cough	10	0	0	9	<1	0

TYKERB in combination with letrozole

In addition to the adverse reactions observed with TYKERB monotherapy, the following adverse reactions have been reported to be associated with TYKERB in combination with letrozole with a frequency difference of greater than 5% compared to letrozole alone. These data are based on exposure to this combination in 654 patients.

Respiratory, thoracic and mediastinal disorders	
Very common	Epistaxis.
Skin and subcutaneous tissue disorders	
Very common	Alopecia, dry skin.

Table 10 Most common study medication related adverse reactions (³ 10%) in 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) and diarrhoea (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%).

DOSAGE AND ADMINISTRATION

TYKERB treatment 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 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 (*see Dose delay and dose reduction — Cardiac events*).

HER2 protein overexpression or gene amplification is necessary for the selection of patients for whom TYKERB therapy is appropriate. Evidence of a previous positive test result for HER2 overexpression or gene amplification should be confirmed before initiating therapy with TYKERB. If historical results 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 should be taken at least one hour before, or at least one hour after food (*see Interactions and 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*).

Consult the product information of the co-administered medicinal product for relevant details of their dosage, contraindications and safety information.

HER2+ over expressing metastatic breast cancer

TYKERB in combination with capecitabine

The recommended dose of TYKERB is 1250 mg (i.e. five 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 Trials*). Capecitabine should be taken with food or within 30 minutes after food.

TYKERB in combination with paclitaxel

The recommended dose of TYKERB is 1500 mg (i.e. six tablets) once daily continuously in combination with paclitaxel. When coadministered with TYKERB, the recommended dose of paclitaxel is 80 mg/m^2 on days 1, 8, and 15 of a 28 day schedule. Alternatively, paclitaxel may be given at a dose of 175 mg/m^2 every 21 days (*see Clinical Trials*).

Attachment 1: Product information for AusPAR Tykerb GlaxoSmithKline Australia Pty Ltd PM-2011-00908-3-4 Final 12 November 2012. This Product Information was approved at the time this AusPAR was published.

Hormone receptor + and HER2+ metastatic breast cancer

The recommended dose of TYKERB is 1500 mg (i.e. six 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 product information of the medicinal product for dosing details.

Dose delay and dose reduction (all indications)

Cardiac events (see 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 institution's lower limit of normal. TYKERB may be restarted at a reduced dose (1000 mg/day when administered with capecitabine and 1250 mg/day when administered with paclitaxel or an aromatase inhibitor) after a minimum of 2 weeks and if the LVEF recovers to normal and the patient is asymptomatic. Based on current data, the majority of LVEF decreases occur within the first 12 weeks of treatment, however, there is limited data on long term exposure.

Interstitial lung disease/pneumonitis *(see Precautions and Adverse Events).*
TYKERB should be discontinued in patients who experience pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are NCI CTCAE grade 3 or greater.

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 paclitaxel or an aromatase inhibitor, 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 paclitaxel or an aromatase inhibitor).

Dose delay and dose reduction (administration with paclitaxel)

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 1500 mg/day when toxicity improves to grade 1 or less. If the toxicity recurs, then Tykerb should be restarted at 1250 mg/kg.

Taxanes are also associated with bone marrow suppression and other toxicities. The full prescribing information for paclitaxel should be referred to for advice on dose delay and dose reduction of paclitaxel.

Children:
The safety and efficacy of TYKERB in paediatric patients has not been established.

Elderly:

There are limited data on the use of lapatinib in patients aged 65 years and older. See Table11.

Table 11 Exposure in Elderly Patients

Patient age (years)	³ 65 years	³ 75 years
Lapatinib + capecitabine (N=198) (EGF100151)	33 (17%)	2 (1%)
Lapatinib + paclitaxel (N=222) (EGF104353)	16 (7%)	0
Lapatinib + letrozole (N=642) (EGF30008)	285 (44%)	77 (12%)
Single agent lapatinib (N=599) (EGF20002, EGF20008, EGF20009, EGF103009)	101 (17%)	24 (4%)

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

Hepatic Impairment:
Patients with severe hepatic impairment (Child-Pugh Class C) should have their dose of TYKERB 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 are no clinical data with this dose adjustment in patients with severe hepatic impairment (see Precautions and Pharmacokinetics – Hepatic Impairment).

OVERDOSAGE

There is no specific antidote for the inhibition of ErbB1 (EGFR) and/or 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*).

Asymptomatic and symptomatic cases of overdose have been reported in patients being treated with lapatinib. Symptoms observed include known lapatinib associated events (see Adverse 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 would not be expected to be an effective method to enhance the elimination of lapatinib.

Further management should be as clinically indicated or as recommended by the Poisons Information Centre (131126).

PRESENTATION AND STORAGE CONDITIONS

TYKERB (Lapatinib ditosylate monohydrate) tablets contain 250 mg mg of lapatinib as ditosylate monohydrate per tablet. The 250 mg tablets are oval, biconvex, yellow film-coated tablets, with one side plain and the opposite side debossed with GS XJG.

TYKERB film-coated tablets are supplied in PA/Al/PVC/Al blister packs of 40 (sample pack), 70, 84 and 168* (2 packs of 84 tablets) and HDPE bottles with child resistant closure packs of 70 and 84 tablets.
*not all pack sizes may be marketed.

Do not store above 30°C. Shelf life at this temperature is 2 years.

POISON SCHEDULE

Schedule 4 – Prescription only medicine

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria 3067

Attachment 1: Product information for AusPAR Tykerb GlaxoSmithKline Australia Pty Ltd PM-2011-00908-3-4 Final 12 November 2012. This Product Information was approved at the time this AusPAR was published.

TYKERB® is a registered trade mark of the GlaxoSmithKline group of companies.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 28 June 2007

DATE OF MOST RECENT AMENDMENT: 13 June 2012

Version 7.0